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THE BLOOD VOLUME EXPANSION PRODUCED BY GELATIN, SERUM ALBUMIN, AND PLASMA

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RECENTLY much interest has been displayed in the use of various plasma volume expanders. Despite this interest, there have been no measurements reported of the relative effectiveness of these various substitutes. In a previous communication it was reported that dextran produced approximately a 1,000 cubic centimeter increase in blood volume which was maintained for at least 8 hours and that at 24 hours there was a 200 cubic centimeter increase in the blood volume (4).

The present report is concerned with the comparison of gelatin, serum albumin, and plasma with the data obtained from the dextran study.

METHOD

In order to obtain comparable results 500 cubic centimeters of 5 per cent gelatin, 500 cubic centimeters of plasma, and 100 cubic centimeters of concentrated serum albumin were given over approximately the same length of time (1 hour). This amount of serum albumin is equivalent to 500 cubic centimeters of plasma. Twenty-six patients on the orthopedic service hospitalized for fractures, dislocations, chronic osteomyelitis, but otherwise in good condition clinically were selected.

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The blood volume was determined by a modification (1) of the method of Hevesy and Zerahn using p^{32} labeled red blood cells and the changes in the blood volume determined by the method reported previously (4). Six patients received plasma, 7 patients gelatin, and 4 concentrated human serum albumin. In no case was any reaction noted.

RESULTS

The results following the administration of gelatin are presented in Table I, in Table II those with plasma, and in Table III those with serum albumin.

In Figure 1 a graphic comparison of the average increases in the blood volume following the various plasma expanders is presented, and the previously reported dextran data are included.

DISCUSSION

Following the administration of dextran, there was reported on the average for the 6 patients studied a sharp initial increase in the blood volume amounting to approximately 1,000 cubic centimeters in 15 minutes and 1,100 cubic centimeters in 45 minutes. Following this the blood volume increment drops to 900 cubic centimeters at 1 hour 15 minutes and then gradually increases to a maximum of 1,350 cubic centimeters at 5 hours. Between 5 and 8 hours there is again a slight decrease,

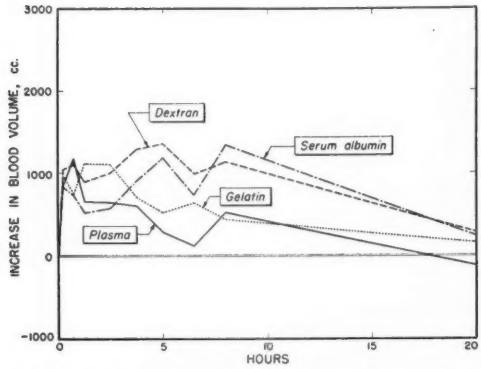

Fig. 1. A comparison of the average blood volume increases produced by administration of dextran, gelatin, serum albumin, and plasma.

the increase being 1,100 cubic centimeters at 8 hours. At 20 hours the effect has almost completely disappeared, there being a net increase of 275 cubic centimeters at this time.

Following the administration of gelatin, the initial average increase for 7 patients is 960 cubic centimeters. Subsequently there is a decrease to 750 cubic centimeters at 45 minutes, there is a second rise to 1,100 cubic centimeters at 1 hour 15 minutes which is maintained for another hour 15 minutes. At 3 hours 45 minutes the volume begins to drop and continues to fall with small fluctuations to average a net increase of 150 cubic centimeters at 20 hours.

In the case of plasma the average initial increase in 6 patients is 830 cubic centimeters and the maximum increase of 1,170 cubic centimeters is reached in 45 minutes. Following this there is a sharp drop to 660 cubic centimeters at 1 hour 15 minutes. This value is maintained until 3 hours 45 minutes, following which there is a rapid decrease ending with a net loss of 130 cubic centimeters at 20 hours.

After 100 cubic centimeters of concentrated serum albumin the average initial increase is 830 cubic centimeters increasing to 970 cubic centimeters in 45 minutes. At 1 hour 15 minutes the increase amounts to 530 cubic centimeters which is maintained for another 1¼ hours. Following this a second rise begins reaching 1,180 cubic centimeters at 5 hours. Another drop occurs at 6 hours 30 minutes and then the maximum increase of 1,340 cubic centimeters is reached at 8 hours. The net increase at 20 hours is 240 cubic centimeters.

Lowell, Cournand, and Richards reported an average plasma volume increase of 520 cubic centimeters within ½ hour after the rapid injection of concentrated human serum albumin, averaging 46 grams per injection, in oligemic and hypotensive patients. At 2½ hours after injection they found no consistent change in the plasma volume. Although no comparison with our studies can be drawn because of the rapid injection of larger amounts of concentrated albumin and the shorter period of observation in patients who were in an unsteady state, the same general trend was noted.

The graph of the average increases in the blood volume demonstrates the differences

TABLE I.—BLOOD VOLUME (C.C.) EXPANSION PRODUCED BY ADMINISTRATION OF GELATIN

Time		Patients							Average
hr.	min.	Ma	Mu	R	Mo	De	H	Du	
15		1354	1002	911	386	1286	1132	650	960
45		741	27	847	425	918	1523	776	751
1	15	1820	1178	1349	590	890	1225	776	1118
2	30	1800	1011	1278	715	907	1141	940	1113
3	45	1374	897	732	465	401	726	336	704
5		965	218	699	435	82	570	680	521
6	30	1184	492	417	445	533	1123	340	647
8		647	286	638	258	375			440
20		228	368	674	271	−289	26	−213	152

TABLE II.—BLOOD VOLUME (C.C.) EXPANSION PRODUCED BY ADMINISTRATION OF PLASMA

Time		Patients						Average
hr.	min.	M	K	P	R	S	H	
15		631	882	2170	−30	359	972	830
45		612	1746	2532	−132	854	1426	1173
1	15	427	461	575	827	306	1249	657
2	30	−205	770	522		537	1625	649
3	45	311	−202	74	854	469	2103	601
5		−195	−193	462	374	251	989	281
6	30	−193	251	−168	264	40	477	111
8		−167	564	230	−14	184	2334	521
20		−276	−309	−221	−814	−69	887	−133

among the four substances studied. Dextran showed the greatest initial increase which is maintained and then reaches its maximal effect at 5 hours and only drops slightly during the ensuing 3 hours. With gelatin the initial increase is not as great and is not as well maintained. The maximum is reached in 1 hour 15 minutes and holds only for another 1 hour 15 minutes and then decreases steadily. After plasma the initial rise is not as great as with dextran or gelatin. The peak is reached in 45 minutes and then decreases rapidly with a net decrease of 130 cubic centimeters at 20 hours. After serum albumin there is the same initial increase as with plasma. Thereafter they differ markedly. After a small increase there is a drop and then a marked and progressive increase with slight fluctuation to reach the maximum at 8 hours.

The colloid osmotic pressure of dextran has been reported as being 1.5 to 2.0 times that of plasma, and the same order of magnitude as a corresponding solution of plasma proteins. While the colloid osmotic pressure of the dextran solution used was not measured, the molecular weight was approximately 50,000. With a concentration of 6 per cent (the actual solution used was 5.855 per cent) this would have a colloid osmotic pressure of approximately 23 millimeters of mercury as compared to 25 millimeters of mercury for plasma. The gelatin solution had a colloid osmotic pressure of 50 to 60 millimeters of mercury. The gelatin and albumin solutions, and possibly the dextran, have colloid osmotic pressures greater than plasma. It can be calculated that in the average individual, the gelatin infused will raise the colloid osmotic pressure of the plasma approximately 6 millimeters of mercury. This is sufficient to produce a 1,220 cubic centimeter increase in a normal individual having a plasma volume of 2,500 cubic centimeters.[1] For the serum albumin the increase in colloid osmotic pressure is sufficient to produce only part of the observed increase in blood volume. Of course this consideration does not apply to the infusion of plasma, and leaves the explanation for part of observed increases due to the plasma, dextran, and serum albumin unexplained.

[1]Calculated on the assumption that the plasma colloid osmotic pressure was 25 mm. Hg, and that after completion of the infusion the plasma volume is 3,000 c.c., and has a colloid osmotic pressure of 31 mm. Hg, it would then require dilution by an additional 720 c.c. to reduce the plasma colloid osmotic pressure to 25 mm. Hg.

TABLE III.—BLOOD VOLUME (C.C.) EXPANSION PRODUCED BY ADMINISTRATION OF SERUM ALBUMIN

Time		Patients				Average
hr.	min.	E	W	B	S	
15		675	318	900	1415	827
45			330	1765	823	972
1	15	338	527	553	688	526
2	30	209	377	708	1000	573
3	45	214	859	1495	1066	908
5		859	899	1547	1428	1183
6	30	224	871	145	1709	737
8		1103	1158	1547	1563	1342
20		36	299	72	680	236

As reported in the previous paper, hematocrits were done on all the blood samples after completion of the infusion. The same discrepancy was again noted as before, in that when the hematocrits were used to calculate red cell volume and plasma volume, an apparent increase in the total red cell volume accompanied the plasma volume increases. When the effect of the substance being infused has disappeared the total red cell volume as determined by the hematocrit also returns to the preinfusion level. Therefore we believe the increase in red cell volume is apparent rather than real and represents an effect on the hematocrit through an unknown mechanism, possibly due to increased trapping of plasma in the packed cell layer in the hematocrit tube.

SUMMARY

A comparison of the blood volume expansion produced after infusion of gelatin, plasma, and serum albumin, using saline as a control has been studied in 20 patients.

Of the substances in this and the previous report dextran showed the greatest initial rise and the longest duration of effect.

With gelatin the magnitude and duration of effect was slightly less than with dextran.

Serum albumin acted differently than the others showing an early sharp rise, then a fall,

and then a delayed but sustained rise to approximately the same maximum increase seen with dextran but occurring later.

Plasma showed the least effect as a plasma volume expander.

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EFFECT OF TISSUE DAMAGE ON THE PLASMA FIBRINOGEN LEVEL

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THE effect of physical trauma on the plasma fibrinogen level has been noted by several workers. Foster and Whipple, after tissue injury and inflammation, Chanutin and associates, after laparotomy, Henriques and associates, after nephrectomy, all showed increased fibrinogen levels 24 hours after the indicated trauma occurred. No samples were taken until 24 hours had elapsed.

In direct opposition to these findings, Mathey and co-workers noted drastically lowered fibrinogen levels during, and immediately following, drastic thoracic surgery. A similar decrease has been observed following abruptio placentae. In this connection it has been suggested that sufficient thromboplastin is washed from the placenta into the maternal blood stream to cause conversion of prothrombin and therefore conversion of fibrinogen to fibrin. If enough thromboplastin is introduced, thromboembolic phenomena could occur as has been shown experimentally by Schneider, but, if the amount of thromboplastin is limited, the reaction could end with the deposition of thin sheaths of fibrin on the blood vessel walls. In this case a decreased plasma fibrinogen level should be observable. Also, since it is logical to expect the liberation of thromboplastin followed by the formation of intravascular fibrin as a sequel to any significant amount of tissue injury, it would seem likely that the elevated 24 hour fibrinogen levels reported by Whipple and Chanutin could well have been preceded by a period of hypofibrinogenemia. In order to explore this possibility, we subjected two groups of rabbits to two types of trauma. The first group was traumatized with a minimum of tissue injury, while the second group was traumatized by a method involving considerable tissue injury.

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MATERIALS AND METHODS

Methods of inducing trauma. Control samples of 10 milliliters of blood were drawn by cardiac puncture on all rabbits just before any manipulations were begun. These were assayed for fibrinogen and designated as zero hour samples.

The 10 series I rabbits were anesthetized with pentobarbital sodium 35 milligrams per kilogram intraperitoneally or 25 milligrams per kilogram intravenously. The abdomen was entered through the linea alba with a minimum of bleeding and the mesentery of the small intestine was pinched with a hemostat until the affected parts became engorged with blood and the animal entered a state of shock as evidenced by deepening of the anesthesia and cyanosis of the mucous membranes. The abdomen was closed in two layers with silk sutures and the animal returned to its cage. One hour, 6 hours, and 24 hours later, 10 milliliters of blood were drawn by cardiac puncture for the fibrinogen assay. At these same times, a similar sample was withdrawn from control animals given the same anesthetic but not subjected to surgery.

The 10 series II rabbits were similarly anesthetized and a tourniquet sufficiently tight to prevent venous return but not tight enough to interfere with arterial supply was placed around one thigh. Then the muscles distal to the tourniquet were traumatized with a rubber mallet by striking 500 times. One hour later the tourniquet was removed. Blood samples were withdrawn by cardiac puncture 2 hours, 4 hours, 6 hours, and 24 hours after the trauma was inflicted.

Determination of fibrinogen. The chemical determination of fibrinogen was carried out by a method designed by one of us (A.H.F.). A fibrin clot was formed by adding 1.0 milliliter of 2 per cent calcium chloride and 2.0 milliliters of thrombin solution (20 units per

TABLE I.—SERIES I RABBITS (WITH MINIMAL TISSUE DAMAGE FOLLOWED BY SHOCK) FIBRINOGEN LEVELS IN MILLIGRAMS PER CENT*

Rabbit No.†	0 hour	1 hour	6 hours	24 hours
4	236	232	440	502
6	300	225	307	224
7	493	445	447	615
8	376	—*	315	503
9	469	241	203	478
10	356	264	—*	362
15	297	283	338	646
16	360	372	375	473
17	302	290	319	669
18	284	245	249	579
Mean	347	289	333	505
Standard deviation	82	74	80	135
Standard error	26	25	27	42
P value‡		>.1<.2	>.7<.8	<.01

*Samples clotted.
†Rabbits 1–3, 5, and 11–14 did not survive the experiment.
‡P values are for the mean fibrinogen level at the given time interval as compared to the mean fibrinogen level at zero time.

ml. in normal saline) to 5.0 milliliters of oxalated plasma diluted with 5.0 milliliters of saline-phosphate buffer.[1] After 1½ hours at 25 degrees C., the clot was broken up and then centrifuged for 10 minutes at 2,500 revolutions per minute. The serum was discarded, and the clot was washed 3 times with normal saline in order to remove the proteins other than fibrin. After the last washing, the clot was carefully rolled on hard-surfaced filter paper to remove excess liquid, placed in a Kjeldahl flask, and its nitrogen content determined. A factor of 5.9 was used to convert nitrogen to protein.

Statistical evaluation. In order to evaluate the significance of the results, the method of Burn was used. The standard deviations, standard errors, and probability values are included in the tables.

RESULTS

Table I contains the data for the series I rabbits. If one considers any probability values under 0.05 as indicating a statistically significant result, one must conclude that no changes in the indicated means are significant except the rise at the 24 hour interval.

Table II gives the same data for the series II rabbits. In this case, not only the rise at 24 hours, but also the falls at the 4 hour and 6 hour intervals are statistically significant.

Table III gives analogous data for the group of control rabbits. It will be seen that none of the changes in the observed means are statistically significant.

DISCUSSION

Two salient facts in our work merit further discussion: (a) the significant decrease in plasma fibrinogen which was shown to take place after considerable trauma to tissues (series II) but which did not occur after relatively bloodless surgery followed by shock induced with minimal tissue damage (series I), and (b) the significant increase in plasma fibrinogen which was shown to occur after both procedures.

The decreased plasma fibrinogen levels which have been observed after abruptio placentae or other abortive conditions as well as during and after thoracic surgery have been attributed to two possible mechanisms: (a) the presence in the blood stream of a fibrinolysin, or (b) intravascular clotting due to thromboplastin gaining access to the circulation. Since the profibrinolysin plasminogen is normally present in plasma it is certainly tempting to assume that an unknown substance may enter the blood stream in abortive conditions, and perhaps during surgery, which is capable of converting plasminogen to plasmin and results in the destruction of fibrinogen. The evidence in favor of this explanation is, on the whole, unconvincing. Conley could not detect a fibrinolysin in his patient with afibrinogenemia. Mathey determined the presence or absence of a fibrinolysin by measuring the time necessary for the clot to lyse. This is, at best, an indirect measure. The time necessary for lysis to occur depends not only on the amount of fibrinolysin present but also upon the amount of fibrin in the clot. Weiner does not sufficiently emphasize or quantitate his fibrinolysin determinations to make them impressive. It

[1] 6.8 gm. KH_2PO_4 plus 1.57 gm. NaOH q.s. to 1 liter with water, then diluted 1 to 5 with normal saline.

TABLE II.—SERIES II RABBITS WITH INTENSIVE TISSUE DAMAGE
FIBRINOGEN LEVELS IN MILLIGRAMS PER CENT

Rabbit No.	0 hour	2 hours	4 hours	6 hours	24 hours
1	219	190	195	204	329
2	242	206	196	208	326
3	227	207	189	165	343
4	304	264	247	229	624
5	224	204	195	165	388
6	392	316	283	258	431
7	258	253	258	232	380
8	466	199	329	355	550
9	352	460	304	299	354
10	316	249	229	243	463
Mean	305	255	244	236	409
Standard deviation	79	84	48	58	100
Standard error	25	26	15	18	31
P value*		>.1<.2	<.05	<.05	<.02

*P values are the the mean fibrinogen level at the given time interval as compared to the mean fibrinogen level at zero time.

TABLE III.—SERIES III CONTROL RABBITS ANESTHETIZED ONLY
FIBRINOGEN LEVELS IN MILLIGRAMS PER CENT

Rabbit No.	0 hour	2 hours	4 hours	6 hours	24 hours
1	470	431	458	440	378
2	546	452	487	487	445
3	300	328	396	420	510
4	256	199	222	308	326
5	295	315	—*	258	301
6	357	271	—*	291	370
7	389	389	—*	479	460
8	238	212	—*	273	314
9	287	243	—*	263	253
Mean	349	316		358	373
Standard deviation	103	93		96	84
Standard error	34	31		32	28
P value†		>.8		>.9	>.8<.9

*Not determined.
†P values are for the mean fibrinogen level at the given time interval as compared to the mean fibrinogen level at zero time.

should also be remembered that the severe cases of hypofibrinogenemia were noted only when the placenta or the lungs were involved in the trauma. Since these two organs have been shown to be the richest in thromboplastin (10), it seems logical to assume that thromboplastin may be involved in the fibrinogen depletion process in the manner of the normal clotting mechanism.

Page and associates and Ratnoff and associates have shown experimentally that extracts of the placenta and brain, rich in thromboplastin, are capable of inducing both low plasma fibrinogen levels and even death due to intravascular clotting. Our work seems to indicate that damage to tissue other than the placenta or lung may also result in decreased plasma fibrinogen levels.

The significant rise which occurred at 24 hours is in agreement with the published literature. It occurred in both series of rabbits but not in the control series. If these elevated 24 hour levels are assumed to be in the character of a rebound, then it may be postulated that release into the circulation of even minute amounts of thromboplastin may stimulate the liver to manufacture more fibrinogen.

The maximum mean fall in plasma fibrinogen which we observed was 22 per cent at 6 hours in the series II rabbits. While this fall is not too impressive, neither was the amount of tissue traumatized. It is conceivable that extensive and bloody surgery may require the infusion of fibrinogen into patients, as suggested by Mathey, to prevent severe hemorrhage.

SUMMARY

1. Bloodless surgery followed by shock induced with minimal tissue damage produced a slight but not statistically significant decrease in the plasma fibrinogen concentration of rabbits.

2. More extensive tissue damage produced a significant decrease in the plasma fibrinogen concentration of rabbits within 6 hours.

3. Both kinds of trauma produced a significant increase in the plasma fibrinogen concentration of rabbits after 24 hours.

4. It is suggested that thromboplastin released from the injured tissues is responsible for the changes seen.

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VENOUS MESENTERIC OCCLUSION IN THE COURSE OF MIGRATING THROMBOPHLEBITIS

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THREE instances of venous mesenteric occlusion in patients with antecedent migrating thrombophlebitis have come to our attention within 2 years. This sequence may be more frequent than is generally recognized. Venous thrombosis develops relatively slowly in contrast to the fulminating course of arterial mesenteric occlusion. There is thus a period, often several days in duration, during which surgical resection of involved bowel may be done with favorable prospects for success. The diagnosis of mesenteric occlusion has always been one of acknowledged difficulty. Knowledge of past episodes of thrombophlebitis in a patient with acute abdominal pain may be a determining factor favoring prompt laparotomy and recovery.

The most common type of thrombophlebitis is one manifestly secondary to surgical operation, delivery, trauma, heart failure, infection, alteration in blood viscosity such as polycythemia, or metastasizing neoplasm. This secondary type of thrombophlebitis not infrequently gives rise to pulmonary thromboses but involvement of other viscera is quite unusual. Recurrences at the same site are frequent but rarely does this process wander to distant superficial veins. Equally familiar is the thrombophlebitis migrans which constitutes the venous component of thromboangiitis obliterans.

Our cases do not fall into either of these categories but represent a third type which appears spontaneously in otherwise healthy individuals. It was first described in 1866 by Sir James Paget and has subsequently been reported under a variety of names. Some of these spontaneous cases exhibit an extraordinary migratory tendency with sequential involvement of segments of widely disseminated veins. This increases the chances of visceral involvement most frequently in lungs or mesentery. When a mesenteric thrombosis occurs the acute abdominal signs obscure the significance of antecedent episodes of peripheral phlebitis. However, if these individuals with a history of migratory thrombophlebitis were recognized as candidates for mesenteric thrombosis, early exploratory laparotomy might establish the cause of their obscure abdominal pain. The attitude of utter pessimism which has long prevailed toward the surgical relief of mesenteric thrombosis should be discarded. Patients with a considerable extent of bowel involved may survive an intestinal resection if their general condition has not been allowed to deteriorate too severely.

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CASE REPORTS

CASE 1. L. J. In July 1947, this 32 year old man developed pain in the left chest, fever, and a pleural friction rub. The roentgenogram showed a patch of pneumonitis. Four days later he noted a "tender knot" in the right popliteal space. The left lung cleared within a week, but meanwhile a similar pneumonitic process appeared at the base of the right lung accompanied by hemoptysis. Thrombophlebitis then became manifest in the opposite leg. His general condition worsened and the inferior vena cava was ligated on August 8, 1947. Later a lumbar sympathetic ganglionectomy was done. He remained well for the next 2 years, except for swelling of his legs in consequence of which he was unable to work.

He was first seen by us on October 8, 1949. Six days previously he had noted diminution in the size of his stools, and frequent bowel movements. For 3 days there had been colicky pain in the lower abdomen and vomiting. On the day of admission he took castor oil which produced 6 or 8 passages of bright red blood from the rectum. Upon admission the abdomen was moderately distended with tenderness in the left lower quadrant and diminished peristalsis, but no palpable masses. Rectal examination showed bright red blood in the lower bowel. A

Fig. 1. Thrombosis of a dilated vein in the mesentery of Case 1. There is edema and hemorrhage in the contiguous fat. The accompanying mesenteric artery appears to be normal. × 12.5.

scout film of the abdomen showed only distention of the ascending and transverse colon. The tentative diagnosis was acute intestinal obstruction due to an unknown cause. He was intubated, given glucose intravenously, and operated upon 8 hours after admission.

First operation (10–8–49). As the abdomen was entered a moderate amount of clear fluid was encountered. The distal half of the descending and proximal sigmoid colon, comprising an estimated distance of 25 centimeters, was involved by a sausage-shaped tumor, deep purple in color, firm and rubbery in consistency. The upper border was well demarcated whereas at the lower border edema extended distally into the entire rectum. The mesocolon of the involved segment was tremendously thickened. Although the nature of the lesion was not clear, it was decided to resect the involved colon. In dividing the mesocolon, multiple thrombi were seen projecting from the veins and there was almost no bleeding from the cut surfaces. The ends of the bowel both above and below the resected segment were clamped and exteriorized since the edema precluded primary suture. No other abnormality of the bowel was noted at this operation.

The resected bowel had a maximum diameter of 10 centimeters and a wall 1.2 centimeters thick. Its midportion was black, blending to a normal color at its proximal end. In the midportion the mucosa was necrotic. Histologically, there was diffuse edema and hemorrhage, especially in the submucosa and mesentery. Many of the larger mesenteric veins and their tributaries showed extensive thrombophlebitis. Arteries and arterioles adjacent to the thrombophlebitic veins were encased in the inflammatory reaction but contained no thrombi or evidence of a primary arteritis (Figs. 1 and 2).

On the fifth postoperative day audible peristalsis having returned, the duodenal tube was withdrawn and the clamp removed from the proximal colostomy. Convalescence then proceeded satisfactorily until the ninth day when, coincident with cessation of drainage from the colostomy, he began to vomit and had severe epigastric pain. On the twelfth day he developed acute vascular collapse and a brisk hemorrhage from the colostomy and a second laparotomy was performed as an emergency.

Second operation (10–20–49). The jejunum showed a lesion identical with that observed in the colon 12 days before. The jejunal mesentery was thickened and no arterial pulsations could be felt. A segment, 35 centimeters in length, was resected and end-to-end anastomosis done. Microscopic examination showed both thrombosis and thrombophlebitis of the small veins in the jejunal wall, as well as the major veins in the mesentery, but no arterial involvement.

On December 9, the colon was reconstructed by end-to-end anastomosis. A temporary fecal fistula healed prior to discharge from the hospital on February 14, 1950. Sections of the deep epigastric artery and vein, and the rectus abdominis and gastrocnemius muscles were biopsied but showed no evidence of vascular disease.

During the following year he was troubled by edema of the lower extremities, but had no manifestations of vascular disease. He has never had claudication, color changes in the feet, or any other symptoms of arterial disease, and his peripheral pulses are always of good quality. On January 18, 1951, he was readmitted with thrombophlebitis of the right leg and abdominal wall which subsided under anticoagulant therapy. In May 1951, he developed a thrombophlebitis of the right internal saphenous vein from ankle to groin. This subsided in 2 weeks without anticoagulant therapy. There has been no further thrombophlebitic episode to May 1952.

Summary. Over the course of almost 5 years this patient has had acute thrombophlebitic lesions successively in the right popliteal, pulmonary, left popliteal, sigmoidal, superior mesenteric, right superficial crural, right circumflex iliac, and right long saphenous veins. Resections of the sigmoid and jejunum were done for episodes of mesenteric thrombosis. There is no histological evidence nor have there been any clinical manifestations of peripheral arterial deficiency.

CASE 2. F. C. B. In May 1949, while driving an automobile this 59 year old man developed pain in the calf of the right leg. This persisted and a tender, red area developed. Later he had cough, dyspnea, and pain in the right chest but no hemoptysis. Ten days after the onset he was hospitalized with the diagnosis of femoral thrombophlebitis and pulmonary embolism. The only residual was some edema of the feet, and at no time did he experience claudication even on strenuous exercise.

Two and a half years later he developed a constant, midabdominal pain and constipation which continued for about 3 weeks and then became more severe and was concentrated in the lower abdomen. He vomited 2 or 3 times and passed flatus, but had

no bowel movements for 2 days prior to our first observation of him on December 21, 1951. There was slight distention and considerable suprapubic tenderness with slight muscle spasm. The laboratory findings were all within normal limits. Barium enema outlined the entire large bowel giving no indication of any abnormality. The patient was intubated but his pain became gradually more intense and unremitting. On the fourth day in the hospital exploratory laparotomy was undertaken.

Operation (12–24–51). Thin, brown fluid escaped as the incision was made. There was a 6-inch segment of gangrenous intestine about 4 feet above the ileocecal junction. Three inches proximally there was a second gangrenous segment. The mesentery was extraordinarily edematous, and as it was divided multiple thrombi protruded from the veins. The bowel wall was greatly thickened but its lumen was patent. Adequate pulsations were felt in the superior mesenteric artery. Three feet of intestine with attached mesentery were resected and anastomosed by end-to-end suture (Fig. 3).

Histologically, the bowel showed extensive edema and hemorrhage with mucosal necrosis and ulceration. The mesenteric veins were occluded with thrombi but there was no evidence of phlebitis. There was no inflammation or thrombosis of mesenteric arteries.

Anticoagulant therapy was employed from the second to the tenth postoperative day. The patient was discharged on January 12, 1952, but returned 10 days later because of left-sided chest pain. Although there were no definite physical or x-ray evidences of pulmonary infarction, he was again placed on heparin and penicillin. Intercostal blocks relieved his pleuritic pain and he has since remained well.

Summary. This patient with no evidence of cardiac or peripheral arterial disease had an episode of thrombophlebitis in the leg complicated by pulmonary infarction and 2½ years later a venous thrombosis of the mesentery of the ileum. The abdominal symptoms developed very gradually over a period of 3 weeks culminating in intense, unrelenting pain. He recovered following resection but had a brief episode suggestive of pulmonary thrombosis 1 month later.

CASE 3. R. P. A white male, aged 59 years, was admitted to the Veterans Administration Hospital, Dallas, Texas, on August 18, 1949, with thrombophlebitis of the left leg. In the course of clinical study a mild hypertensive cardiovascular disease with evidence of an old myocardial infarction was discovered.

He re-entered the hospital on March 6, 1951, with cramping discomfort in the upper abdomen associated with nausea, anorexia, and constipation for 3 weeks. There was considerable abdominal tenderness and an indefinite mass in the suprapubic region. Gastrointestinal x-ray film and barium enema showed diverticulosis but were otherwise negative. The patient's abdominal complaints continued intermittently. On the fifth day he had severe cramps and vomited several times. On the eighth day he became jaundiced and on the ninth his condition changed abruptly for the worse. He collapsed with signs of peritonitis and died on March 16, 1951.

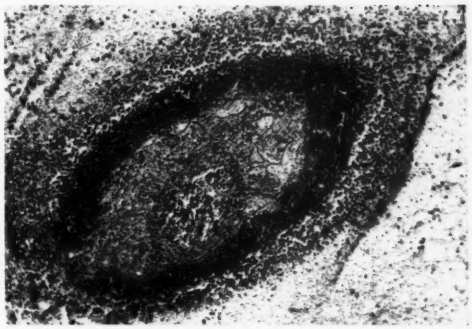

Fig. 2. High power (× 65) of section through the submucosa of the intestinal wall in Case 1. The inflammatory changes in the wall and in perivenous tissues are evident. This is the only case of the 3 reported which shows extensive thrombophlebitis. In the others the lesions are predominantly phlebothromboses.

Autopsy. There was diffuse peritonitis. There was a 200 centimeter segment of gangrenous small bowel beginning about 30 centimeters above the ileocecal junction with contiguous mesentery thickened by edema and hemorrhage. The superior mesenteric and portal veins were occluded by an adherent, soft, laminated thrombus. More recent, red thrombi propagated into the liver and throughout the tributaries of the superior mesenteric vein. The vena cava and the hepatic veins, and the mesenteric, hepatic, and splenic arteries were free of thrombi. Histologically, the infarcted ileum showed necrosis of the mucosa, edema in the submucosa and hemorrhage in the muscularis. The veins of the bowel as well as the major branches of the superior mesenteric were occluded by thrombi, and surrounded by a minor perivascular inflammatory reaction. The superior mesenteric and portal veins at the site of attachment of the organizing thrombi were distorted by collagenous scarring, lymphocytic infiltration, and a minor degree of hemosiderin deposition.

There was evidence of coronary arteriosclerosis and an old myocardial infarction of the interventricular septum and the anterior surface of the left ventricle. Mural thrombi adhered to the area of infarction as well as to the endocardium of the left atrium. The spleen contained a small area of infarction.

Summary. This patient experienced a femoral thrombophlebitis 19 months prior to his entrance into the hospital with rather vague abdominal pains and constipation. After 9 days of observation he collapsed quite suddenly, and autopsy showed a gangrenous ileum resulting from thrombosis of the

Fig. 3. Gross specimen of ileum resected in Case 2. The bowel has been sectioned and the cut surface turned upward. Note the enormous thickening of the wall due entirely to edema and hemorrhage. The lumen remains patent even in the area of most severe involvement and the patient did not have clinical signs of complete intestinal obstruction. The thickening of the mesentery can also be seen. × 1.4.

superior mesenteric and portal veins. This patient differed from the preceding in having evidence of arteriosclerotic heart disease with old myocardial infarction. The clinical course of the mesenteric thrombosis presented ample opportunity for surgical resection had the diagnosis been suspected.

SIMILAR REPORTED CASES

Partial review of the literature reveals 14 cases in which a migrating type of primary thrombophlebitis culminated in venous mesenteric thrombosis. Doubtless some cases have been overlooked. The reports indicate a predominant incidence in the male sex. The youngest patient was a boy of 14 years reported by Birnberg and Hansen and, insofar as ages are stated, they range otherwise from 21 to 43 years. Our 2 patients in the sixth decade of life are therefore the oldest on record. Some of the reported cases are of unusual interest. The patient of Sullivan and Walske had thrombophlebitic episodes involving veins of the forearm, both legs, the lung, and the abdominal wall for 9 years before the terminal event in the mesentery. Two patients reported by Berry and Bougas are likewise extraordinary. The first (Case 1 and 1A in their report) had involvement of various superficial veins during a 4 year period, a remission for 7 years, then survived a resection of the jejunum for mesenteric thrombosis and 3 years later a second resection for involvement of the ileum. The total span of the disease in this patient was 15 years at the time of Berry's report. A second patient (Case 11) is remarkable not only for recurrent thrombophlebitic episodes including a successful resection of the ileum, spanning a 15 year period, but because of his amazing family history. His 2 brothers also had venous mesenteric thrombosis. In one it was a complication of appendectomy. The other followed a spontaneous thrombophlebitis in the leg and is similar to those which concern us. We include it together with 2 cases reported by Moorhead and Abrahamson, 3 by Gerber, and 1 each by Barker, Fischer, Krieg, and Stern, making 14 cases reported in the literature similar to our own. The only patients who have survived have been 2 clinically mild and nonsurgical cases (11), those resected by Berry and associates, and by ourselves. In most instances the diagnosis was not made until autopsy or so late that only exploratory laparotomy was done.

There is reason to believe that as more cases are recognized in the resectable stage the salvage rate can be improved. Resection of involved bowel may not, of course, be curative since recurrent thrombotic episodes may be anticipated. Whether prolonged anticoagulant therapy may prove to be practicable in this disease remains to be proved. Dicumarol therapy requires continuous supervision with prothrombin determinations, and for all that we know it may have to be continued for the lifetime of the patients. One of Berry's patients remained symptom-free for 29 months on dicumarol medication. The other was reported to have discontinued therapy some time during the first year after operation and was well at 11 months. Our first patient has had anticoagulants only for brief periods when his superficial phlebitis was active. Our

second patient received anticoagulants during the early postoperative period but has not been followed long enough to determine the eventual outcome.

CLINICAL PICTURE

The typical course of the disease may be constructed from reported cases and our own experience. A previously healthy individual, most frequently a male under the age of 45, develops a nonsuppurative inflammation in a medium-sized superficial vein of an extremity usually the lower limb. The first episode is likely to be trivial. The signs of phlebitis disappear for an interval varying from a few weeks to several years only to reappear subsequently. These episodes are repeated sometimes at the original site, sometimes at a new one. In approximately one half of the cases deep veins become involved and then edema may become a persistent feature. In about 1 case in 4, manifestations of pulmonary vein involvement are present. Other visceral complications are relatively uncommon, and in their absence the disease appears to run a benign course without inherent mortality.

Mesenteric venous thrombosis in this disease does not present as a fulminating catastrophe. Our patients did not enter the hospital until 6, 21, and 21 days respectively after the onset of their symptoms. The primary abdominal discomfort is followed, as the thrombosis extends in the mesentery, by pain of great severity. One of the notable features is that the severity of the pain is disproportionate to any objective abdominal signs. There is a notable absence of the signs of peritoneal irritation. There may be tenderness over an involved segment of intestine but not enough to warrant suspicion of an acute intraperitoneal infection. Vomiting is inconstant and tardy in its appearance. Only at an advanced stage does mechanical obstruction occur. In the early stages the bowel wall is thickened but the lumen remains patent. Therefore distention is not a prominent feature. Blood may be passed by rectum as a result of necrosis of the intestinal mucosa. Because in its early stages the disease does not present characteristic symptoms, an appreciation of the implications of previous thrombophlebitic episodes is important in diagnosis. Clinical laboratory tests cast no light upon alterations in the mesenteric veins. X-ray examinations likewise reveal no abnormality until complete occlusion of the bowel occurs. Time expended upon these clinical investigations may prove very costly to these patients by delaying the surgical exploration upon which ultimate definitive diagnosis will usually depend.

PATHOLOGICAL FEATURES

The gross appearance of the involved intestinal segment immediately suggests a vascular occlusion. The involved segment is imperfectly demarcated, shading from dark purple in the center to a normal pink in both directions. The diameter of the involved bowel is increased by merit of the increased thickness of the wall rather than by dilatation of its lumen. It feels to the surgeon like a firm tumor. The lumen may contain blood if the hemorrhagic mucosa is ulcerated. The contiguous mesentery has a thick, rubbery consistency and contains ecchymotic areas. As it is sectioned thrombi project from the severed vessels. There is little bleeding from the cut edges of mesentery, but arterial pulsations may be felt beyond the limits of gross involvement. Evidently there is an associated element of spasm in the arteries of the thrombosed mesentery. Most of the thrombi are dark red and are easily withdrawn. Attached thrombi may be found in the larger collecting veins suggesting that propagation from these sites may be responsible for shutting off collateral circulation. The apparent uniformity in the age of the thromboses which were seen in our material indicates that a propagating process is more likely to occur than an intermittent involvement of smaller tributaries.

The microscopic changes are those of hyperemia, hemorrhage, and edema of the entire intestinal wall and mesentery. The larger mesenteric veins, as well as those within the bowel, are plugged with thrombi by far the majority of which appear to be recent, since only occasional fibroblasts are observed. The thinned venous wall may contain varying degrees of acute inflammation.

It would appear that mesenteric thrombosis may arise on the basis of pre-existing phlebitis as in our first case. In the second case there was thrombosis of a dilated but otherwise normal vein. Although multiple sections were examined, nothing could be found which could be interpreted as thrombophlebitis. In the third case there were minor alterations at the site of attachment of the oldest thrombus but even these were more consistent with an organizing thrombus than with a phlebitis. Occasionally in our sections the arterioles of the intestinal wall in the areas of mucosal ulceration showed a mild inflammatory reaction but in no instance was the arterial bed thrombosed.

POSSIBLE RELATIONSHIP TO THROMBOANGIITIS OBLITERANS

Consideration has been given to whether this lesion represents an early phase of Buerger's disease. We do not believe this to be the case. Thromboangiitis by definition involves both arteries and veins. The typical thrombophlebitis migrans may occasionally appear coincidently with the onset of intermittent claudication and the other evidences of arterial insufficiency, but there have been only isolated reports of phlebitis as the initial manifestation. The most dramatic example of this was reported by d'Abreau, but may not have been true Buerger's disease. His patient at the age of 22 began a series of episodes of thrombophlebitis in the legs and abdominal wall. Forty years later he developed claudication, cold livid feet, and poor peripheral pulsations. This progressed to gangrene requiring amputation. Autopsy showed an advanced arteriosclerosis with thrombosis of the aorta extending into the iliac arteries. The case reported by Johnson is more typical. His patient had recurrent episodes of phlebitis in the foot and calf for 11 years and then developed claudication along with other signs of Buerger's disease.

Increasingly it is being recognized that Buerger's disease may have visceral complications. Averbuck and Silbert attributed death in 22 of 47 autopsied cases to visceral thromboembolic incidents. Cohen and Barron collected 15 cases of mesenteric thrombosis in patients with thromboangiitis obliterans. Close scrutiny, however, indicates that arteriosclerosis played a major role in most of these cases and that the association with Buerger's disease was merely coincidental. Moreover the mesenteric lesions described were for the most part arterial occlusions and were not confined to the veins as in the cases discussed herein.

SUMMARY

1. We report 3 cases of venous mesenteric thrombosis occurring in patients with antecedent migrating thrombophlebitis in superficial veins of the extremities. Fourteen similar cases are collected from the literature.

2. The early peripheral manifestations are characteristically widely disseminated with respect both to site and time, bland in their nature, and confined exclusively to the venous side of the vascular tree.

3. Visceral involvement is not uncommon in the course of this disease, the greatest predilection being for the lung and the next for the mesentery. The visceral lesions like those in the superficial veins have a mild inception, propagate slowly, and do not involve the arteries.

4. The clinical diagnosis of mesenteric thrombosis has inherent difficulties. A history of previous spontaneous thrombophlebitis may be significant. Exploratory laparotomy may be the only means of establishing the diagnosis sufficiently early for successful resection.

5. The ultimate outcome in this disease is uncertain. Reasons are cited for disbelieving that it represents a stage of thromboangiitis obliterans.

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THE PROTHROMBIN IN THE NEWBORN

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EVEN though tremendous progress has been made in the control of the hypoprothrombinemias, much uncertainty still exists concerning the prothrombin in the blood of the newborn infant. When this agent is determined by the one stage method, it is found to be normal except for a brief period during the first week of life, whereas when measured by the two stage procedure it remains low for many weeks and only attains the adult concentration at the end of 1 year. These puzzling and contradictory findings have not been satisfactorily explained nor have they been adequately evaluated clinically. With the development of the concept that the prothrombin in adult human blood exists only partly in a free or active state, a new approach to the problem of the prothrombin in the newborn is offered (10, 12). In the present investigation, the free and total prothrombin as well as the labile factor were quantitatively determined in the maternal, the cord, and the infant's blood when vitamin K was given prepartum and when it was omitted.

METHODS

Blood was obtained from the mother and baby by venipuncture within 10 minutes after delivery. A silicone-coated syringe and needle were used and the blood transferred to test tubes coated with silicone. Cord blood was collected directly into silicone-coated test tubes and mixed with either sodium oxalate or citrate solution immediately after the cord was cut. The blood was chilled by placing it in an ice bath and the analyses were made within 1 hour after the blood was collected.

Prothrombin time (*one stage test for determining prothrombin*). The original procedure (6) was followed exactly except for two modifications: the blood was collected and mixed with sodium oxalate in silicone-coated glassware and 0.01 molar solution of calcium chloride was used instead of 0.02 molar solution. Every lot of thromboplastin (acetone dehydrated rabbit brain) used in this study gave a prothrombin time of 12 seconds when tested on fresh normal human plasma.

Total prothrombin time. The one stage prothrombin time measures only the free or active prothrombin and is not influenced by the inactive prothrombin (prothrombinogen). To estimate the total prothrombin, it is necessary to convert the prothrombinogen to active prothrombin. This may be done either by storing the oxalated plasma in an open glass container at 4 degrees C., or by clotting the plasma after the removal of the platelets by high centrifugation. The accompanying diagram (Fig. 1) helps to explain the underlying reactions.

During storage in glass, the prothrombinogen becomes converted to free prothrom-

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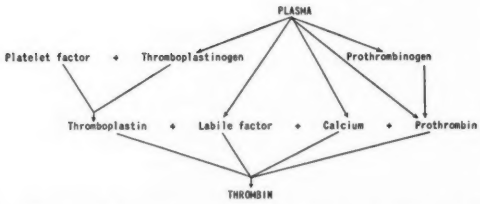

Fig. 1. The basic factors in the clotting mechanism. The prothrombinogen when in contact with glass is slowly converted to free prothrombin on storage at 4 degrees C. and rapidly at 37 degrees C. during coagulation. When plasma is depleted of platelets and then clotted, little prothrombin is consumed, while all of the prothrombinogen is converted to the free state. The active prothrombin of the serum, therefore, is much greater than that of the plasma and its prothrombin time much shorter.

bin. Since the concentration of the labile factor also is altered, i.e. diminished during storage, it is necessary to restore the latter, before the prothrombin of stored plasma can be determined by the prothrombin time test. To do this, a small quantity of rabbit plasma (deprothrombinized by means of tricalcium phosphate) which is a rich source of labile factor is added to the stored plasma. The determination is as follows: To 0.09 cubic centimeter of stored oxalated plasma, 0.01 cubic centimeter of deprothrombinized rabbit plasma is added. The prothrombin time of the mixture is determined by the standard procedure of adding thromboplastin and calcium chloride. For normal bloods, values from 8 to 9 seconds are obtained.

The second method for determining total prothrombin depends on the removal of platelets and then clotting the plasma in glass. Due to the lack of platelets, only a trace of thromboplastin is formed and therefore no detectable amount of prothrombin is consumed. But under the conditions in which this clotting occurs, all of the prothrombinogen is converted to free prothrombin. Consequently the serum has a much higher prothrombin activity than the original plasma. In a recent paper (10), we presented evidence to show that this increase of activity in serum is due to an actual increment of prothrombin.

In carrying out the test, 4.5 cubic centimeters of blood are mixed with 0.5 cubic centimeter of 0.2 molar solution of sodium citrate in a silicone-coated test tube. The blood is centrifuged for 10 minutes at 4,000 revolutions per minute in an Angle centrifuge. The plasma is carefully removed by means of a silicone-coated pipette and transferred to another silicone-coated heavy walled test tube. This is centrifuged for 30 minutes at 12,000 revolutions per minute. One cubic centimeter of this plasma is transferred to a glass test tube mixed with 0.1 cubic centimeter of 0.3 molar solution of calcium chloride and incubated at 37 degrees C. The fibrin is removed as it forms by wrapping it about a glass stirring rod. After the fibrinogen has all been clotted, the tube is incubated 15 minutes more. The prothrombin of the serum is determined as follows: To a mixture of 0.1 cubic centimeter of deprothrombinized rabbit plasma, 0.1 cubic centimeter of thromboplastin reagent and 0.1 cubic centimeter of 0.02 molar solution of calcium chloride, 0.1 cubic centimeter of serum is added and the clotting time accurately measured. The total prothrombin time, like in the first procedure, is 8 to 9 seconds.

The total prothrombin of every sample of blood was determined by both methods except when the quantity was insufficient. From the data which are presented in Table I it can be seen that the results of the two methods agree well.

Labile factor. The determination of labile factor is based on the following principle: Oxalated human plasma when stored at 4 degrees C. losses labile factor, which quantitatively accounts for the observed increase in the prothrombin time. To estimate the concentration of labile factor in a sample of plasma, a measured amount is added to a fixed volume of a standard stored human plasma, and the prothrombin time of the mixture determined. When 1 volume of normal deprothrombinized human plasma is added to 9 volumes of stored plasma (having a prothrombin time of 40 seconds), the resulting mixture has a prothrombin time of 17 to 21 seconds. The plasma is deprothrombinized with tricalcium phosphate which quantitatively removes prothrombin by adsorption but does not remove any detectable amount of labile factor. The details of the test have been described recently (8).

TABLE I.—THE PROTHROMBIN TIME, TOTAL PROTHROMBIN TIME, AND LABILE FACTOR OF THE MOTHER'S, INFANT'S, AND CORD BLOOD

Type of blood	Prothrombin time sec.	Total prothrombin time†		Labile factor sec.
		sec.	sec.	
No vitamin K given				
Mother	14	8½	8½	15½
Infant	15½		15	16½
Cord	16	16½	15½	16½
Mother	13½	8	8½	17
Infant	15		15	17
Cord	15½	14	15	16
Mother	12	9	9	15
Infant	14		13	16
Cord	14	16	16	15
Mother	13½	8½	8½	16
Infant	13½		14	17
Cord	14	14	14½	17
Mother	13½	8	8½	15
Cord	17	15	16	18
Cord	17½	20	17½	18
Cord	16½	14	15	15
Cord	14	17	16	16
Cord	15	15	15	17
Cord	15	16	17	18
Cord	14	14½	15	18½
Cord	13½	14	13½	18
Cord	15	15	13½	16
Cord	17		17	
Vitamin K given*				
Mother	12	9	8½	18½
Infant	12		12½	19
Cord	12	12½	12½	20
Mother	11½	8½	8½	17
Infant	11½	13	13½	18
Cord	11½	13	13	17
Mother	12½		8	17
Infant	13		13½	17½
Cord	13		13½	17½
Cord	12	13	12	17
Cord	12	13	12½	18
Cord	12½	12½	12½	18
Cord	12½	13	12	17½
Cord	12	12	12½	15
Cord	12	12½	12½	15½

*An ampule of synkayvite containing 10 mgm. was given intravenously on admission to the hospital. Delivery usually occurred 6 to 14 hours later.
†The total prothrombin time recorded in the first column was obtained on the serum from deplateletized plasma, while those of the second column from plasma stored in glass.

RESULTS

From the data presented in Table I, a number of deductions can be made. When the mother receives a water soluble vitamin K compound such as synkayvite prior to delivery, the prothrombin time of the maternal cord and infant's blood is normal (12 seconds). This may be interpreted to mean that the "prothrombin activity" is normal and equal in all three bloods. If no vitamin K is given, the cord blood almost invariably shows a moderately prolonged prothrombin time. The same was found in the 4 babies who were studied immediately after birth. Since it appears that the baby's and the cord blood are very similar, it was felt justifiable to study mainly cord bloods. It should be noted that even the mother's prothrombin time may be slightly prolonged at the puerperium when no vitamin K is given. In no instance was a hyperprothrombinemia observed in the mother's blood as Norris and Rush reported. After the administration of vitamin K, the prothrombin time became 12 seconds consistently, but never was shorter.

Most unexpected was the finding that the prothrombin time and total prothrombin time are essentially the same in the cord and in the infant's blood. Significantly, the administration of vitamin K to the mother brings the prothrombin time and the total prothrombin time of the baby to 12 seconds, but not any lower. In marked contrast, in the mother the total prothrombin time is 8 to 9 seconds even when the prothrombin time is slightly prolonged. Thus, the total prothrombin time is entirely normal in the maternal organism, whereas in the newborn infant the total prothrombin time is only equal to the free prothrombin time.

The labile factor was found to be roughly the same in both the mother's and in the baby's blood. Vitamin K appears to have no influence on its concentration. This agrees with our previous findings that in experimentally induced hypoprothrombinemia by vitamin K deficiency, the labile factor remained normal (6). Stefanini, likewise, found only a slight depletion of this factor in 7 cases of hypoprothrombinemia of the newborn. Randall and Randall also concluded that lack of

labile factor was not the cause of the prothrombin deficiency in the newborn infant.

DISCUSSION

These findings correlated with older observations throw a new light on the problem of the prothrombin in the newborn. When the available vitamin K is adequate, the fetus can apparently produce prothrombin readily, and maintain a prothrombin time equal to that of the adult. When the mother is not given vitamin K in addition to that furnished by the diet, the fetus generally does not secure sufficient quantity of the vitamin to have a prothrombin time of 12 seconds. In fact even the maternal blood may have a slightly prolonged prothrombin time under these conditions. This is not surprising since we have recently observed that the adsorption of the natural vitamin K_1 from the intestinal tract is exceedingly small in the dog (11), and this is likely to be true also in the human. If the one stage method determines free or active prothrombin, it can be concluded that the fetus when provided with vitamin K can synthesize prothrombin and can maintain the reactive or free prothrombin at the same level as is found in adult blood.

The observation that the prothrombin time and total prothrombin time are equal is evidence that all of the prothrombin in the newborn infant is in the free or active state. Since the administration of vitamin K to the mother brings the concentration of only the free prothrombin to normal and does not shorten the total prothrombin below 12 seconds, it suggests that the infant at birth lacks the ability to form prothrombinogen. Therefore, while blood from an adult contains both free and inactive prothrombin, the infant contains only free prothrombin. From the data of earlier studies it has been calculated that the free prothrombin of plasma from an adult constitutes only about one-fourth of the total prothrombin. While a newborn baby with a prothrombin time of 12 seconds has a concentration of free prothrombin equal to that of adult blood, it nevertheless has only about 25 per cent as much total prothrombin as the matured human subject since its free prothrombin constitutes the entire store.

It is interesting to note that the prothrombin in a newborn baby as determined by the two stage method varies roughly from one-fourth to one-third of the adult concentration. Brinkhous and associates found a range of 14 to 39 per cent. Owen and his group, Helltman Shettles, and their co-workers and Javer and, Macri reported similar findings. They further observed that while the administration of vitamin K did somewhat elevate the prothrombin of the blood, it rarely brought it above one third of the normal adult value. In contrast, the prothrombin time of both the mother and the infant as seen from the present findings is normal provided the supply of vitamin K is adequate.

Thus, while the results obtained with the one and two stage procedures appear utterly contradictory, a simple explanation can be offered to show that this is not true. As pointed out previously, the two stage test does not differentiate between free and total prothrombin (7). Due to the various manipulations in the test, most of the prothrombinogen is presumably converted to the free state. The two stage method, therefore, measures essentially total prothrombin; and the finding that the prothrombin concentration of the newborn baby as determined by this method is approximately one fourth of normal is entirely in accord with this explanation.

The concept that human blood contains only part of the prothrombin in the active state and that this fraction only is measured by the one stage method, while the two stage procedure, like the total prothrombin time test, measures the total prothrombin, eliminates the necessity of postulating additional factors which supposedly govern the convertibility of prothrombin. Since the concentration of labile factor is the same in the cord as in the maternal blood, it cannot be held accountable for the observed differences in the prothrombin activity between the maternal blood and that of the infant.

Aside from these theoretical considerations, it is obvious that the results obtained by the two stage method on human blood must be interpreted with caution. Since the prothrombin at birth as determined by this test is only 25 per cent of the adult value, a

separate standard of normal for the newborn must be set up, but immediately another difficulty is encountered because prothrombin gradually attains the adult value during the first 12 months. The standard, therefore, must be corrected for age, but this cannot be done until the necessary data become available. If it should be found that the rate of increase in total prothrombin is not the same in all infants, a future complication arises. The correlation of the results of the two stage method with hemostasis is obviously difficult. A prothrombin level of 25 per cent of normal denotes the beginning of a bleeding tendency in the adult, but this same value in the newborn is normal and cannot be increased with vitamin K. Since the two stage method, even when carried out by experienced workers, shows a range of 240 to 450 units per cubic centimeters for normal adult blood, it is easy to understand why it is difficult to determine accurately the fluctuations of the prothrombin concentration that occur during the first week of life.

On the basis of numerous studies, it has been established that the one stage test is a reliable guide for estimating the prothrombin activity of the newborn physiologically. Even the advocates of the two stage method tacitly admitted this when they employed the one stage test for determining the vitamin K requirements of the newborn infant.

It is highly probable that it is primarily the active prothrombin on which hemostasis depends; consequently when an infant has a prothrombin time of 12 seconds, its hemostasis appears to be as normal as that of the adult even though its total prothrombin is only 25 per cent. The infant, nevertheless, is presumably in a somewhat precarious situation. It probably has little or no store of vitamin K, and none is probably immediately available from the digestive tract. The metabolic demands deplete the free prothrombin rapidly, and if one postulates that the prothrombinogen functions as a reserve, the lost prothrombin cannot be promptly replaced because of the absence of the latter. Hypoprothrombinemia, therefore, is common shortly after birth unless the mother is given extra vitamin K.

It is interesting to speculate whether this hypoprothrombinemia that normally occurs in the newborn is accidental or purposeful. No answer can be given since one only knows that while hypoprothrombinemia may bring about serious bleeding in the infant, the incidence of the true hemorrhagic disease of the newborn is very low. The complete lack of prothrombinogen in the early life of the infant is difficult to explain since the function of this substance has not been determined. Since the agent is also absent in the common laboratory animals such as the dog and rabbit, it may perhaps represent one of the last steps in the evolution of the clotting mechanism. An investigation is now in progress studying the free and total prothrombin in infants during the first year of life with the aim of establishing when and how rapidly the prothrombinogen attains the adult level.

SUMMARY

The prothrombin time of cord and infant's blood was found consistently prolonged when the mother did not receive extra vitamin K prepartum. Even a slightly prolonged prothrombin time was observed in the maternal blood. The administration of vitamin K brought the prothrombin time of the cord, infant's, and mother's blood to normal.

The total prothrombin, which in the normal human adult consists of free and inactive prothrombin (prothrombinogen), was found quantitatively unchanged in the parturient mother. In the newborn baby, no prothrombinogen could be demonstrated. The prothrombin time and the total prothrombin were found equal, thus indicating that all of the prothrombin of the infant is in the active stage. The ineffectiveness of vitamin K to increase the total prothrombin indicates that the infant is unable to form prothrombinogen and the absence of this substance may account for the low prothrombin found with the two stage method.

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VULVAR FLUORESCENCE IN NORMAL AND ABNORMAL PREGNANCY

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AN intriguing newly recognized phenomenon useful in obstetrical and gynecological diagnosis and prognosis has been termed vulvar fluorescence or luminescence. We now know that the illumination of the female pudendum by ultraviolet light elicits a number of particular colors which relate to the woman's hormonal status, yet these hues are not visible without this specific excitation. Although ultraviolet light has been employed for years in the biological sciences, its potentialities in gynecic medicine are only now becoming appreciated.

Ultraviolet light is also called Wood's light or "black light." An understanding of the properties of ultraviolet light requires the recollection that light may be considered as energy of wave motion. The wave lengths, or distance between successive crests, are generally recorded in angstrom units; i.e., 10^{-7} millimeters. Particular colors correspond to certain limited ranges of wave lengths in the visible spectrum considered to extend from 7,000 angstrom units for red, to 4,000 for violet, with orange, yellow, green, and blue between. Near ultraviolet may be represented in the spectrum by the zone from 4,000 to 3,100 angstrom units where middle ultraviolet light causing sunburn begins. Far ultraviolet light, noted for its germicidal effect, begins at about 2,800 angstrom units and approaches x-rays which are in the region of much shorter wave lengths. Although we have noted that the edge of the visible purple extends to 4,000+ angstrom units for a certain few humans, the invisible range of the spectrum can be considered the near ultraviolet range and beyond.

Fluorescence is the property of certain substances to emit light of different wave lengths from the light which they absorb when irradiated. This allows the absorption of light of one wave length; e.g., near ultraviolet, with the re-emission of light of a different (usually longer, and therefore visible) wave length. Hence, the luminescent object is actually a light source in itself. With few exceptions, the re-emitted light is of very low brightness (intensity).

Fluorescence and luminescence are synonymous for our purpose. All living tissues are known to fluoresce but it is not generally realized that this fluorescence contains all the visible spectrum colors with certain hues predominating.

This study of vulvar fluorescence was undertaken to consider the phenomenon of tissue luminescence as it applies to diagnosis and prognosis in normal and abnormal pregnancies. The normal patients studied were pregnant in various stages of gestation or in the early puerperium. In addition to this group, cases of hydatidiform mole, chorionepithelioma, ectopic pregnancy, spontaneous, missed, and therapeutic abortion were examined under near ultraviolet illumination.

MATERIAL AND METHODS

Two hundred women were chosen for study. The criterion for selection was clinical evidence of pregnancy, possible current pregnancy or recent pregnancy. Approximately 415 different observations of vulvar fluorescence were made on these patients, and at each observation a color sketch was made to record the findings. Examination of the woman's vulva and perineal area was made in near darkness at the time of admission, prior to vaginal or speculum examination. Whenever possible, serial observations were recorded in individual patients to evaluate the type and significance of color changes.

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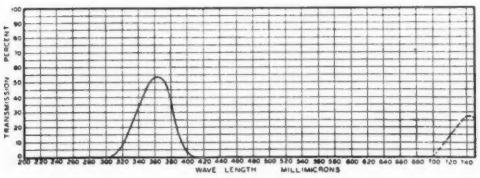

Chart 1. Ultraviolet transmission chart.

The demonstration of tissue luminescence requires an energy source emitting "light" of wave lengths longer than (below) 3,300 angstrom units. The range 3,650 to 4,000 angstrom units is the most satisfactory. However, a conventional mercury vapor lamp with a peak output of 3,650 to 3,663 angstrom units (near ultraviolet) is adequate for most clinical studies. We have also employed a 2 kilovolt mercury arc for more intense irradiation. The arc is an excellent source but it has the disadvantage of not being portable because it requires both a water and air-cooling mechanism.

Filtration of the ultraviolet is always required for the elimination of as much of the lamp-generated visible red and purple as possible. A cutoff close to and below 3,650 angstrom units will suffice for practical purposes, although the edge of visible purple extends slightly beyond. The Corning 5874 filter fulfills this purpose fairly well as is shown by the ultraviolet transmission chart (Chart 1). The faults of this particular filter are its relatively low transmission of ultraviolet light of 3,650 angstrom units or better, and a poor cutoff in the far blue range of normal visibility. A sharp-cutting filter with higher (greater) transmissibility would be more desirable, but this is difficult to obtain commercially.

In a previous paper (2), we reviewed some of the technical and practical problems involved in any consideration of vulvar fluorescence colors in obstetrics and gynecology. A number of deficiencies generally inherent in the filters currently available were discussed. Certain of the physiological factors relative to perception and appreciation of color by the observer were also evaluated. These are an especial problem where low luminosity is the rule.

It must be understood that the woman's vulva does not "glow in the dark" nor does it "light-up" under ultraviolet irradiation, as Novak would imply. In the low intensity illumination possible with the present day commercial "black lights," however, distinct but rather faint colors can be seen. The lack of agreement regarding the hues and shades of color depend, in addition to those outlined previously, upon the eerie effects and individual interpretation of the colors. It is even likely that some disagreement is attributable to minor degrees of color blindness of certain observers.

At any rate, it is well established that a unique fluorescence of the vulvar tissues (*intrinsic* fluorescence) is demonstrable from puberty to the menopause, with the production of a striking range of colors. (*Extrinsic* fluorescence also results from the presence of various materials on the skin and mucous surfaces.) Moreover, these colors have been roughly correlated with ovarian function, pregnancy, and vaginal bleeding. Furthermore, they can be elicited, we believe, by relatively simple equipment. By way of analogy, one might say that it is not necessary to employ a delicate weighing instrument in order to estimate a patient's poundage for most clinical purposes inasmuch as a simple but reliable balance will prove to be adequate.

The basic intrinsic and extrinsic colors of vulvar fluorescence, and their changing pattern, can be demonstrated successfully in near-darkness with any of several portable ultraviolet lamps now available fitted with either a Corning 5874 or Kopp 41 filter and employing either a General Electric or Westinghouse No. CH_4 mercury vapor lamp. A number of these combinations are now commercially available. Elimination of other light and dark adaptation are required of the observer.

Although nonfluorescent additions caused by "leakage" of the filter do occur, experience has taught us to discount them in our observations. Where particular precision is required, a combination of glass filters, quartz-nickel filter, or plastic viewing filters may be used.

OBSERVATIONS

We still find it practical to differentiate six fundamental colors in vulvar fluorescence. These were first referred to by Margolese and MacDonald and Margolese as: (1) *deep purple*, (2) *purple*, (3) *green*, (4) *yellow*, (5) *brown*, and (6) *red*. (We shall adhere to the gross original nomenclature in this article although we recognize the indefiniteness of certain of these terms.) It has been shown that prior to puberty and after the menopause the predominant vulvar colors range from *yellow* to *brown*. During the reproductive era, and particularly during pregnancy, striking and characteristic color variations of *purple* and *deep purple* appear. Some slight individual variations have been noted, and the color being deeper and more pronounced in patients with heavy skin pigment. However, this does not prevent an accurate diagnosis in a large majority of patients.

PREGNANCY

The characteristic color changes observed in pregnancy and at the termination of pregnancy are similar regardless of the stage of gestation or the method of delivery. A very *deep purple* is the predominant and most striking color seen in the pudendum of the normal pregnant woman throughout gestation. This hue is classically distributed across the fourchette and around the labia minora in such a fashion as to constitute a dark, almost "eggplant-colored" ring. Occasionally, one sees a *deep purple* ring also about the urethral meatus (Fig. 1).

A lighter color, *purple*, is frequently seen to extend peripherally over the labia majora and for a varying distance toward the thighs and posteriorly even beyond the anus. This coloration may, in some cases, be quite extensive (Fig. 2). A basic *brown* background may be noted over the labia and in the folds about the clitoris in pregnancy as in the nonpregnant state.

Age and degree of parity are not important in the observation of intrinsic vulvar fluorescence in pregnancy. The typical perineal fluorescence colors, which appear early in gestation and which are the basis for the diagnosis of pregnancy, increase slightly but definitely in intensity and extent of pattern with the advance of gestation. We have tried but have never been able to produce the characteristic *deep purple* of pregnancy by the administration of estrogen to a nonpregnant woman; nor have we been able to intensify significantly a *purple* or *deep purple* in a normal gravid woman even though massive doses of estrogen were administered.

The following observations, although not specific in the diagnosis of pregnancy, are interesting when noted in the examination of pregnant patients under ultraviolet light. They deserve at least passing comment. Normal pubic hair does not undergo color changes during pregnancy but appears under ultraviolet light "as though it had been lightly dusted with flour" (1). Fungus infections, as on the skin, may cause silvery, orange, or even green fluorescence of the hair. Leucoderma, leucoplasia, wide scars, and verruca appear as dull gray or brownish areas and do not participate in the color changes described. Leucorrhea, in the absence of bleeding, often appears as yellow or orange. Striae and varices are seen as dark lines or streaks under ultraviolet illumination. However, they are not accentuated by light of shorter wave length as they are by long wave length illumination (infrared.)

PUERPERIUM

Following abdominal *or* vaginal delivery, a sequence of color changes regularly occurs. Chief among these is the rapid disappearance of *deep purple* from all areas. This is usually complete within 4 days. A lighter color, *purple*, remains diffusely distributed. Vivid *red* appears on the second or third postpartum day. It has been our experience that blood appearing as initial bleeding does not fluoresce but appears black. When bleeding continues over a period of days, regardless of its etiology, *red* fluorescence appears and persists as long as bleeding continues (Fig. 3).

Smearing of lochial discharge, we believe, accounts for the wide distribution of the red across the perineum. Retention of this hue within the folds of the introitus and beneath the clitoris is apparent for a number of days. *Red* may be observed in the bleeding asso-

ciated with pregnancy, the puerperium, dysfunctional bleeding states, cancer of the cervix uterus, and during menstruation. In every instance, this fluorescence color seemed to be superficial and could, in part, be wiped away. We interpret this as the removal of blood or blood products. We are unable to confirm that it represents true tissue luminescence, as suggested by MacDonald and Margolese, and by Greenblatt. *Purple, green, yellow,* and *brown,* it must be remembered, are intrinsic hues and do not disappear, even in part on swabbing. Other fluorophors from rectal and vaginal soilage, lubricants, medicaments, and powders must be avoided or removed for an accurate appraisal of the intrinsic skin luminescence.

Green, and very rarely *yellow,* appear about the fifth to the seventh day postpartum as a mottled or streaked replacement of areas of *deep purple* previously described. These new colors are most frequently seen anteriorly between the labia, about the urethral meatus and clitoris. They seldom persist for longer than 10 to 14 days. These evanescent hues apparently have no relationship to obvious trauma or ecchymosis (Fig. 4).

After the first week following delivery, less *red* is seen. Its disappearance coincides with the subsidence of lochia and the resumption of a more vigorous perineal hygiene. Baths and douches, we believe, help to eliminate this color (Fig. 5).

An orange color, usually beneath the prepuce, is presumably due to smegma. This, like *red,* can be wiped away. Intertriginous fungus infections may also cause an orange or silver fluorescence which is also superficial. No especial color has been related to vaginal moniliasis or trichomoniasis.

ABORTION

With either spontaneous abortion or therapeutic interruption of pregnancy, color changes similar to those following delivery ensue. It does not seem to matter whether evacuation of the uterus is accomplished vaginally or abdominally. The striking *deep purple,* characteristic of pregnancy, is lost after the fourth or fifth day following interruption of the gestation.

The vulvar color variations, observed in threatened abortion under near ultraviolet light, have been most interesting because of possible diagnostic and prognostic potentialities implied. We believe that if the *deep purple,* which is customarily seen in normal pregnancy, is still maintained in the labia minora and fourchette, the presence of bleeding and even cramps may not regularly forecast the termination of pregnancy.

In spite of bleeding and pain, if a color pattern typical of pregnancy persists, one may offer a more favorable prognosis than if *deep purple* were lost completely and *green* or *yellow* noted. In the former instance, hormone therapy may aid in the salvage of the pregnancy. In the latter case, it is probably too late for such therapy. Needless to say, at this stage of study of vulvar fluorescence, we would not recommend dilatation and evacuation, oxytocics or uterine instrumentation on the basis of a single observation or even a changing color pattern.

When the history and clinical findings present an ill-defined gynecological lesion, for example salpingitis versus ectopic pregnancy, vulvar fluorescence has often aided us in the establishing of the correct diagnosis. Pelvic inflammation and its accompanying vascular engorgement do not duplicate the colors described for pregnancy. Similarly, the termination of an early pregnancy, whether uterine or tubal, coincides with the color variations outlined. Even fetal death in utero late in pregnancy has been confirmed by loss of *deep purple.*

The number and type of cases studied in this series are presented in Table I, together with certain of our results.

COMMENT

The fallibility of this method of diagnosis has been demonstrated by the occasional lack of intensity of *deep purple* in apparently normal gestation. Repeated observations, however, will frequently obviate this difficulty. For example, the single observation of a patient in the process of abortion may not provide adequate information as to the trend. In any case, it must be remembered that ultraviolet light is an adjunct method and

Fig. 1. Spread of deep purple.

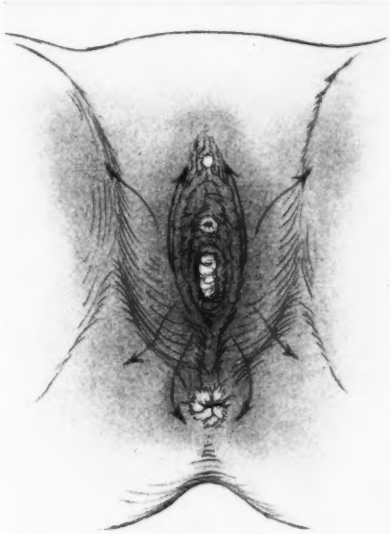

Fig. 2. Spread of purple.

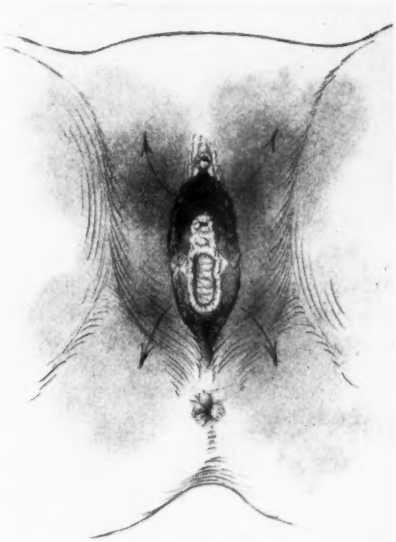

Fig. 3. Spread of red.

Fig. 4. Spread of green.

must be correlated, therefore, with the history and physical findings.

Diagnostic errors. The false diagnosis of pregnancy occurred 6 times in this series. Three false positives and 3 false negatives are recorded. Subsequent investigations revealed hyperplasia of the endometrium in 2 cases. This we considered indicative of either hy-

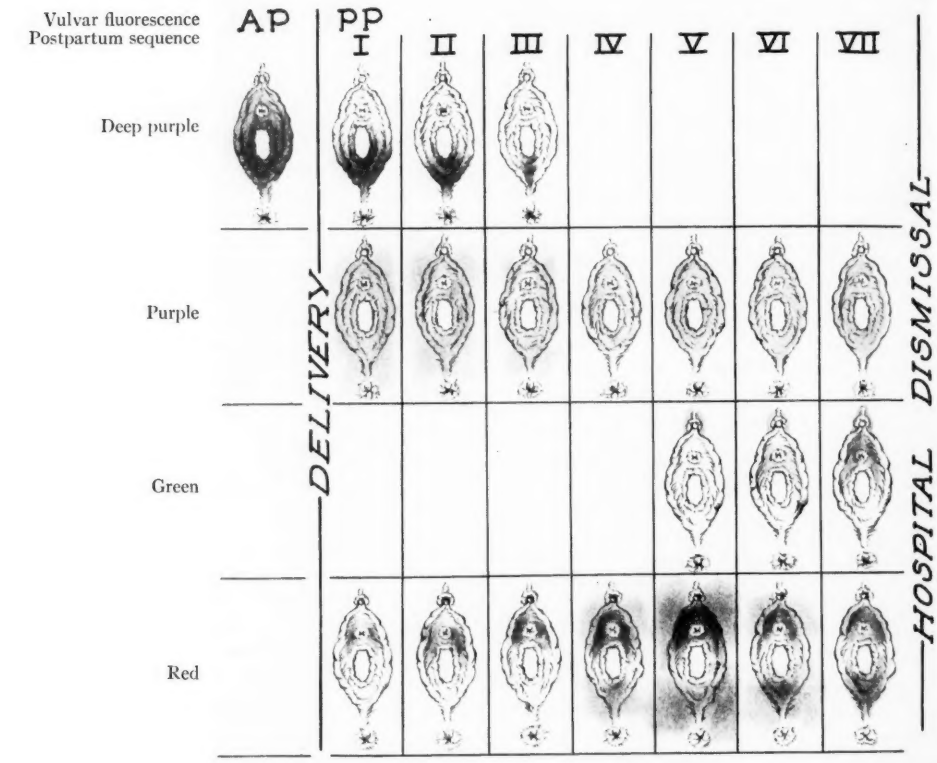

Fig. 5. Chronology of color change postpartum.

perestrinism or unopposed estrogen effect causing prolonged estrin stimulation of the endometrium. A third patient presented functional amenorrhea of 1 to 2 months. We failed to diagnose established pregnancy correctly in 3 cases. Two of these cases were advanced gestations without apparent abnormality. We cannot adequately explain these inaccuracies at this time.

Threatened abortion. The use of vulvar luminescence as a guide for therapy in threatened abortion has been suggested. As an example, 1 of our patients, a woman who for 3 months presented very normal signs and symptoms of pregnancy, and in whom *deep purple* was seen under conventional near ultraviolet light to the pudendum, experienced slight to moderate vaginal bleeding. No pain was reported. In 1 week, the *deep purple* had receded. She was given massive doses of estrogen and adequate sedation and was kept at complete bed rest. In approximately 10 days the bleeding had checked, and although we found that it required 3 weeks for the return of *deep purple*, a wide reappearance of this hue occurred and the patient continued without other eventuality to term. She was ultimately delivered of a normal, living infant. The placenta showed an old area of marginal separation of a fairly sizable degree.

Many obstetricians are enthusiastic about the value of hormone therapy in the salvage of pregnancy in threatened abortion. The employment of vulvar fluorescence may be a

considerable aid in such hormone management. Even where *deep purple* is fading, however, we do not agree with Greenblatt that the presence or absence of *red* is a deciding diagnostic factor. We have emphasized that the appearance of *red* is linked with external evidence of continued bleeding or sanguineous discharge. Even very minimal bleeding may result in the appearance of this color. We feel rather that the extent of *purple* and the intensity of *deep purple* might be a better measure of the need for substitution or supportive hormone therapy in a jeopardized pregnancy.

In contrast to Greenblatt's findings, we saw vivid *red* together with the characteristic hues of pregnancy herein described at some phase of all of our 11 cases of proved ectopic pregnancy. Vivid *red* on the vulva also invariably occurred in each of 10 cases of carcinoma of the cervix or endometrium presenting even minimal bleeding. Further studies on vulvar fluorescence in cases of genital cancer and dysfunctional uterine bleeding are in progress.

The patient's complexion is often important in evaluating vulvar fluorescence because the degree of pigmentation may modify the observation of intensity of color. Contrary to Goodman's observations, we believe the skin of the negress does fluoresce. Patients who show a facial "mask of pregnancy" and who exhibit increased pigmentation in other areas of the body disclose a greater intensity of *purple* and *deep purple* under ultraviolet light. This makes the diagnosis of pregnancy easier in dark-skinned women. Similarly, a spread of *purple* laterally and posteriorly around the anus is characteristic of many cases of pregnancy, even in the rare absence of *deep purple* at the labia minora, as visualized in early or late weeks. This diffuse pattern is commonly seen in women of dark coloring, brunettes, and particularly in melanotic individuals. In women of light complexion, *deep purple* and *purple* may be less extensively present, but *deep purple* is characteristically seen in the fourchette. This is true even early in the first trimester.

One might wonder whether the elevated titers present in hydatidiform mole or chorionepithelioma might be associated with an intensification of certain colors, such as the *deep purple* of pregnancy. Observations on 3 cases of hydatid mole and 1 lethal choriocarcinoma with increased chorionic gonadotrophin revealed either colors of average pregnancy (before evacuation) or hues of abortion. Increased vulvar intensities were not noted.

A curious accentuation of *purple* and *deep purple* could sometimes be obtained by stretching the skin and mucous surfaces. This was particularly noticeable at the fourchette. It is believed, therefore, that care should be taken to observe any given area without physical distortion of the tissues when employing ultraviolet irradiation.

TABLE I.—VULVAR FLUORESCENCE IN NORMAL AND ABNORMAL PREGNANCY

	No. of cases
Pregnant patients	178
Normal (pregnant by UV light) — 123	
Normal pregnancy but inaccurate report of "nonpregnant" due to failure of appearance of vulvar fluorescence colors of pregnancy	3
Abnormal (UV signs of loss of pregnancy and/or abortion) — 55	
Incomplete abortion — 31	
Tubal abortion — 11	
Missed abortion — 9	
Hydatidiform mole — 3	
Chorionepithelioma — 1	
Nonpregnant patients (not pregnant by UV light)	19
?-Pregnant, but negative by vulvar fluorescence — 16	
Inaccurate diagnosis of pregnancy by vulvar fluorescence — 3	
Endometrial hyperplasia — 2	
No apparent pathology — 1	
Total	200

False negative diagnosis of pregnancy by ultraviolet light is recorded in 3 cases or (1.5 per cent) of the cases studied. A false diagnosis of pregnancy occurred in 3 cases (1.5 per cent) of the total series of 200 cases.

SUMMARY

Observations of vulvar fluorescence under near ultraviolet light were made in 200 women to determine their value as a diagnostic procedure in normal, abnormal, and suspected pregnancy.

Typical color findings in normal pregnancy, the puerperium, chorionepithelioma, ectopic pregnancy, abortion, and hydatidiform mole are presented.

These preliminary observations suggest that the method is a definite aid in the

diagnosis of pregnancy and abortion and may assist in determining the need, under various circumstances of pregnancy, for hormonal or other definitive therapy. Further study of vulvar fluorescence in clinical obstetrics and gynecology seems indicated.

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RESTORATION OF FLEXOR POWER TO THE FLAIL ELBOW BY TRANSPLANTATION OF THE TRICEPS TENDON

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RECONSTRUCTION of the upper extremity is a constant, fascinating problem to orthopedic surgeons. While arthrodesis is often performed upon the wrist and shoulder to give functional activity, the immobile elbow joint seldom could be used to transmit motion distally. It is a major disability in the functional mobility of the upper extremity. The motion of utility here is flexion. The transplantation of the flexor mass described by Steindler (3) has been the most valuable, and almost only, means of restoring flexion to the elbow. Far too often, patients are found to have no mass of hand and wrist flexors, or extensors that could be moved to give flexion of the elbow joint. This was the problem which was confronted that stimulated consideration of another source of motor power.

The short tendon of the triceps muscle is motivated by three strong heads. The long head and the lateral head are easily mobilized from the humerus. The medial head is closely adherent to most of the posterior aspect of the humerus. Shortly after the radial nerve passes the lower edge of the teres major muscle and rounds the humerus, it is closely bound by the medial and lateral heads of the triceps muscle. The motor nerves are given off in this area (Fig. 1). If the tendon of the triceps muscle could be freely mobilized with most of the medial head attached to it, a good motor unit with an ample range of transplantation could be obtained. The triceps muscle power could then be used to restore the motion of supination and flexion of the elbow by means of transplantation about the lateral aspect of the humerus into the tendon of the biceps muscle at its point of insertion into the radius.

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Accordingly, a case was selected for this operation. E.B., a 14 year old white male, had a difficult birth resulting in flaccid paralysis. The right upper extremity was useless because of complete absence of any flexor power at the elbow. The arm could be elevated 95 degrees at the shoulder. The forearm was in pronation. The triceps was present and could be rated as normal. Circulation of the extremity was good. The patient was an intelligent, co-operative subject. Operation was performed on February 20, 1950.

With the patient lying on his left side, the right arm was draped for free motion. No tourniquet was used during the procedure. The skin incision was started distal to the olecranon. It passed proximally over the lateral aspect of the olecranon before curving medially, and then extending over the distal two-thirds of the posterior arm in a long curve (Fig. 2). The skin and subcutaneous tissues were dissected back freely to expose the triceps muscle, ulnar nerve, and lateral intermuscular septum. By sharp dissection, the triceps tendon was detached from the olecranon insertion. It was dissected from its muscular fibers to a level approximately 1 inch above the epicondyles. The periosteum was incised at that point and the medial head stripped from the posterior aspect of the humerus. Care was taken to isolate the radial and ulnar nerves to prevent damage. The medial head was covered by suturing the edges together to form a tube of the triceps muscle.

A second incision was made transversely across the antecubital space from the medial aspect to curve distally at the border of the brachioradialis muscle (Fig. 3). The tendon of the biceps was isolated and dissected free to its insertion into the radial tuberosity. It was then split longitudinally. The two inci-

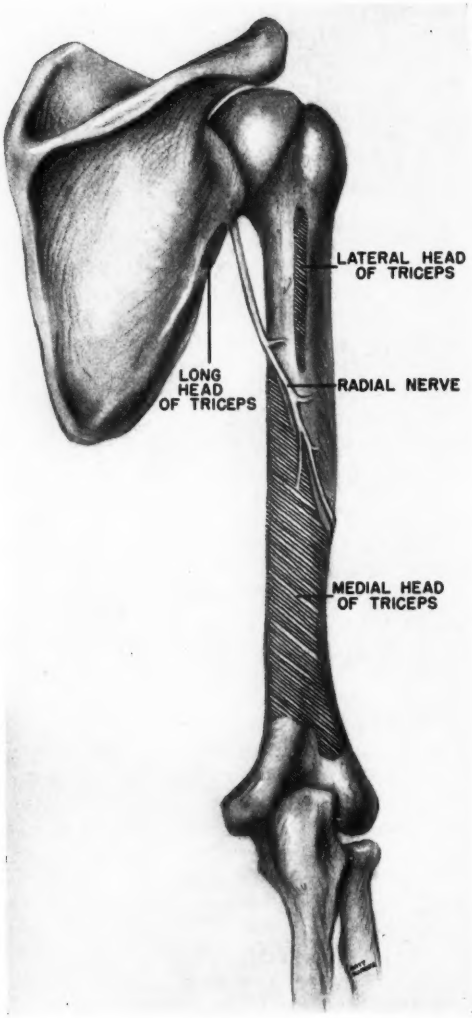


Fig. 1.

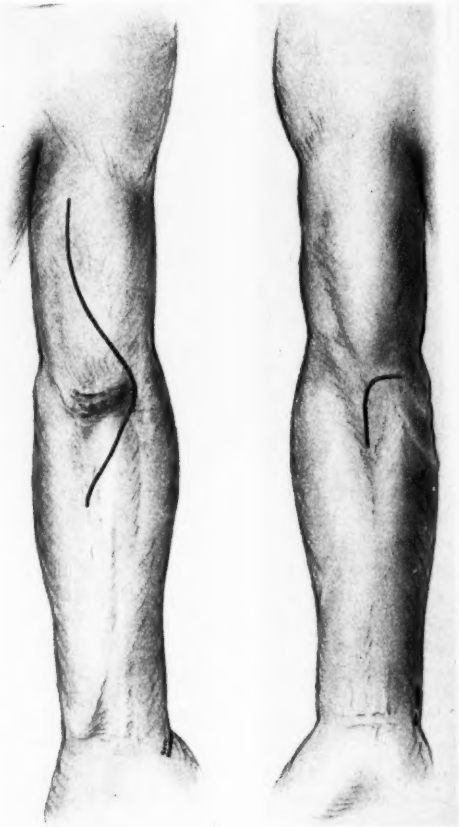


Fig. 2.

Fig. 3.

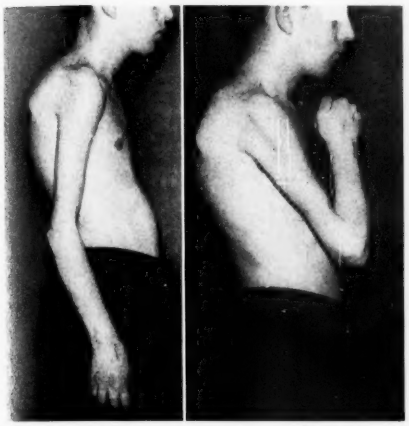
Fig. 4.

Fig. 1. The motor branches of the radial nerve are given off in the area between the medial and lateral heads of the triceps muscle.

Fig. 2. The long curvilinear incision avoids pressure points of the elbow and gives adequate exposure.

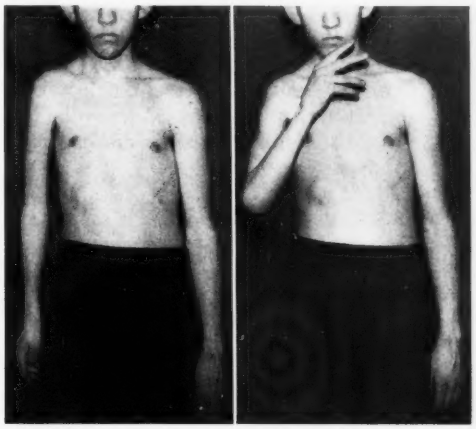
Fig. 3. Only a small incision is necessary to expose the volar aspect.

Fig. 4. The tendon of the mobilized triceps tendon is woven through the biceps tendon with the elbow in flexion.



a b

Fig. 5. a, A flexion deformity of minimal degree has remained. b, Excellent range in flexion at the elbow has been the result.



a b

Fig. 6. a, There is no cosmetic defect with the arm at rest. b, The transplanted triceps muscle now moves the hand into a position of useful function.

sites were connected by blunt dissection to form a tunnel. Through this, the triceps tendon and muscle were passed. Its new position was superficial to the radial nerve. The triceps tendon was passed through the longitudinal split in the biceps tendon, and sutured under tension with the elbow in flexion (Fig. 4). A posterior molded splint held the position of elbow flexion with forearm supination, and the arm was bound to the chest with bandages.

At the end of the fourth week following operation, the splint and bandages were removed. Active motion was started. By the eighth postoperative week, active flexion of the elbow against gravity was easily performed. The range at that time was from 105 degrees to 35 degrees. The right upper extremity became an integral part of his useful functions. It is used freely and without thought as to possible limitation. Power of flexion has developed although gravity still supplies the only extension in the elbow joint. At the end of the first postoperative year, the range of active motion against gravity was from 160 degrees to 35 degrees (Figs. 5 and 6). By supinating the forearm, he is able to hang up his clothes. He is also able to use crutches for walking by holding the crutch tightly adducted to the thorax.

There is no doubt in the author's mind that this specific transplant has been attempted by other clinics. However, the transplantation of the triceps tendon was an independent thought in this clinic. During the month following operation, an intensive search of the literature was made. It failed to reveal any paper dealing with this subject listed in the *Quarterly Cumulative Index Medicus*. The only mention of the potentiality of using this type of transplant is found in an orthopedic textbook by Steindler (4) published in 1940. He concluded this operation to be of doubtful value.

It was with great interest that mention of this procedure was found in the 1948 edition of Bunnell's *Surgery of the Hand* (1). The author knows that Bunnell has successfully transplanted the triceps muscle for flexion of the elbow in 2 cases. The technique of operation described is approximately the same as that presented in this article. Bunnell brings the transplanted triceps beneath the radial nerve. He also finds it necessary to prolong the tendon with fascia. Excellent function has been the result (2).

SUMMARY

1. An additional method of providing flexor power to the flail elbow has been described in

the transplantation of the triceps muscle tendon into the biceps muscle tendon at the radial tuberosity.

2. One case has been presented in which this type of transplantation was used. The period of postoperative observation has been longer than 2 years.

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MITRAL VALVE SURGERY

A Critical Analysis

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THE surgical attack upon mitral stenosis began in America in 1929, when Cutler and Beck operated upon 7 patients who had mitral stenosis. Their results were so disappointing that no further impetus was generated until after the Second World War when Harken (8) became interested in the surgical amelioration of the mechanical obstruction in mitral stenosis. At that time his approach was indirect, and the surgical attack upon the valve proper was termed by him a commissurectomy with "selected insufficiency." This was an effort once again to open the commissures of the mitral valve and relieve the serious complications of pulmonary hypertension. His surgical results as reported were not encouraging and shortly thereafter, in 1949, Sweet and Bland (10) reported on a by-passing operation in which the azygos vein was anastomosed to the inferior pulmonary vein in an effort to decompress the pulmonary system's hypertension into the general venous bed. Bailey, of Philadelphia, in 1949, gave mitral valve surgery its greatest impetus with his mitral commissurotomy, in which a small curved knife was used to cut the anterior lateral and posterior medial commissures of the mitral valve. This procedure was later modified by Harken (7), in what he termed a "finger fracture," accomplishing a fracture of the commissures with similar results as those of Bailey. The immediate postoperative results in these patients were most encouraging and resulted in a widespread interest in the surgical treatment of mitral stenosis.

This study was conducted with reference to the following points: (a) the extent and duration of the amelioration of the symptoms of the disease after surgical therapy, (b) whether or not the incised mitral valve reseals or remains open, and (c) whether correlation exists between the pathological change in the mitral valve and the postoperative results.

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PATIENT MATERIAL

There have been 30 patients followed by the cardiovascular service. Nine patients have been followed postoperatively from 6 months to 1 year by means of cardiac catheterization and clinical study. The mitral valve area was computed by indirect means using the formula of Gorlin and Gorlin, and this computed area compared with that found by finger palpation at surgery. Preoperative and postoperative hemodynamic studies were used to aid us in estimating the changes effected in these patients by surgery.

PATHOLOGIC AND SURGICAL CORRELATION

Despite the fact that the hemodynamics of mitral stenosis is not completely explained on a simple mechanical basis, the surgical approach must be based on a mechanical concept. Harken (8) has indicated that the anterior leaflet of the mitral valve is the major leaflet and acts as a water shed as well as preventing regurgitation, so that on ventricular contraction the blood is baffled into the aorta. The posterior leaflet is also important in preventing regurgitation into the left auricle. An incision through the posterior leaflet would cause much less severe insufficiency than through the anterior, but certainly enough to compromise the surgical result.

The normal mechanism of closure of the mitral leaflets can be thought of as two spinnaker sails ballooning in opposite directions to coapt in the midline and so close the orifice. These leaflets are kept from complete inversion by the chordae tendineae and the

TABLE I.—PATIENT WITH TYPE I VALVE

D.R.H. No. 513204, V.J., 32 yr. old male

	Preoperative		Postoperative (23 weeks)	
	Rest		Rest	Exercise
PC	S/D	30/19	20/12	35/15
mm. Hg	M	26	16	24
PA	S/D	66/33	45/22	92/45
mm. Hg	M	48	28	69
MVA cm.^{2}		0.60	1.27	1.15

PC, pulmonary capillary pressure.
PA, pulmonary artery pressure.
MVA cm.^{2}, mitral valve area in square centimeters.

papillary muscles. Cicatricial change in either the chordae tendineae or the papillary muscles will lead to a shortening of the guy wires of these ballooning structures and to poor coaptation and a faulty closure of the valve orifice. When the valve is attacked by rheumatic fever, the early pathological changes are restricted to the commissures and the free edges of the mitral valve with shortening of the chordae tendineae and papillary muscles. The superior portions of the valve leaflets remain pliable and mobile. After the commissures are opened, these valves once again approximate the normal mechanism of closure. This form of pathological change is classified by us as a type I valve. However, as the disease progresses, the valves become more and more rigid by involvement of the superior portion until in the second stage of the pathological progress these valves are stiff, cardboard-like shelves and are no longer pliable and sail-like. When the commissures are cut, the leaflets are stiff and no longer can move freely although the commissures do not hold them. The valves themselves are partially fixed, and the resultant opening is physiologically less than the anatomical opening created by the surgeon. This condition we classify as a type II valve. The third type of pathological change observed in the mitral valve is a calcification superimposed upon the diffuse fibrous replacement of the mitral valve leaflet. This third type is even more rigid than the second type and leads to a much poorer mechanical opening than either the first or second. The importance of the operative classification of valves into pathological types can be easily illustrated by 2 cases: one representing a return to normal clinical status, and the other showing only moderate clinical improvement. The first patient (Table I), who had a type I valve, has had a complete remission of symptoms and has unlimited exercise tolerance but the hemodynamic study 4 months after the operation showed that the pulmonary artery and capillary pressures though markedly decreased were still above the normal range. The calculated mitral valve orifice had increased from 0.60 to 1.27 square centimeters as a result of the operation. During exercise the patient was free of symptoms, but there was a moderate rise in pulmonary capillary pressure, a marked rise in pulmonary artery pressure, and no change in calculated valve orifice. The fact that the calculated valve orifice remains the same at two pulmonary capillary pressure levels suggests that this pliable valve opens to a maximum under low auricular pressures and an increase in the auricular pressure causes no further increase in the size of the orifice.

TABLE II.—PATIENT WITH TYPE III VALVE

D.R.H. No. 511557, 34 yr. old male

	Preoperative		Postoperative (27 weeks)	
	Rest		Rest	Exercise
PC	S/D	43/28	27/15	51/26
mm. Hg	M	34	23	48
PA	S/D	55/33	44/23	68/38
mm. Hg	M	43	32	51
MVA cm.^{2}		0.50	0.66	0.97

PC, pulmonary capillary pressure.
PA, pulmonary artery pressure.
MVA cm.^{2}, mitral valve area in square centimeters.

The second patient (Table II), who had a type III calcified valve, has had moderate clinical improvement. When studied 6 months postoperatively by cardiac catherization his pulmonary artery and capillary pressures were still elevated although they had significantly decreased from the preoperative levels. The calculated valve orifice had increased in size from a preoperative area of 0.50 to 0.66 square centimeter at rest. With exercise there was a marked rise in pulmonary capillary, and artery pressures and the valve orifice increased to 0.97 square centimeter. These figures may

TABLE III

Case No.	Pulmonary capillary pressure		Pulmonary artery pressure		Area of mitral orifice (sq. cm.)		Type of valvuloplasty	Path. type of valve	Clinical estimations	Postop. mo.
	Preop.	Postop.	Preop.	Postop.	Preop.	Postop.				
1	36	12	44	23	0.7	1.1	Cut	II	Good	10
2	28	21	31	29	0.3	0.4	Fracture	II	Fair and unsat.	4
3	25	22	30	27	1.3	1.3	Dilated	I	Unsat.	7
4	34	23	43	31	0.5	0.7	Fracture and cut	III	Good	7
5	26	16	48	28	0.6	1.3	Fracture and cut	I	Excellent	4
6	29	22	34	32	0.6	1.1	Cut	I	Good	2
7	20	12	28	20	1.1	1.8	Cut	I	Good	4
8	19	18	28	27	1.0	0.9	Fracture	II	Excellent	7
9	29	32	45	50	0.9	0.8	Fracture	II	Excellent to good	7

be interpreted as indicating the relative fixation of a stiff type III valve whose functional opening is not markedly changed by freeing the commissures. That the commissures are free and the valve leaflets can be forced open is shown by the increase in the calculated valve area as the left auricular pressure increases. This may explain the inability of the surgeon to correlate his interpretation of the size of the mitral valve orifice which he has created at operation with the calculated postoperative functional valve size.

RESULTS

In order to determine the permanency of the results of mitral valve surgery, catheterization studies were made every 6 months when possible in an effort to determine whether the valve healed and scarred down again or whether it remained open. There are 9 patients (Table III) in this group who have been studied postoperatively from 2 to 10 months. These 9 cases represent 3 different and distinct types of surgical attack upon the mitral valve, for this too was of interest since we did not know which procedure offered the best results with the least risk. Therefore the valves of these patients were not only cut by means of a Bailey knife but also fractured by digital pressure, and one was dilated as originally reported by Souttar. The patient whose valve was dilated (Case 3) was improved for 4 months, but since has returned to her preoperative status, both clinically and by catheterization studies.

That these patients have all been improved clinically is undeniable, but on examination of the pulmonary artery and pulmonary capillary pressures one is not so confident of the results. Without exception in types II and III valves (Table III, Cases 1, 2, 4, 8, and 9), the pulmonary pressures have not fallen to normal and the functional mitral valve area is considerably less than the anatomical opening created by surgery. In 2 patients (Table III, Cases 8 and 9), both type II valves, 7 months postoperatively, the mitral valve area is less than the preoperative size and the pulmonary artery pressures are greater or the same. Furthermore, upon exercises, as previously illustrated (Tables I and II), the pressures climb to 2 or 4 times normal levels. The accuracy of the indirect computation of mitral valve area is still not fully determined, but direct pressures cannot be dis-

TABLE IV.—SUMMARY OF CLINICAL EXPERIENCE WITH MITRAL VALVULOPLASTY

	No. cases	Per cent
Total	30	
Deaths	2	
Mortality rate		6.6
Embolism postoperatively	2	6.6
Complications postoperatively		
Pericardial effusion	1	
Breast abscess	2	
Embolic phenomena	2	
Excellent to good clinical results		77

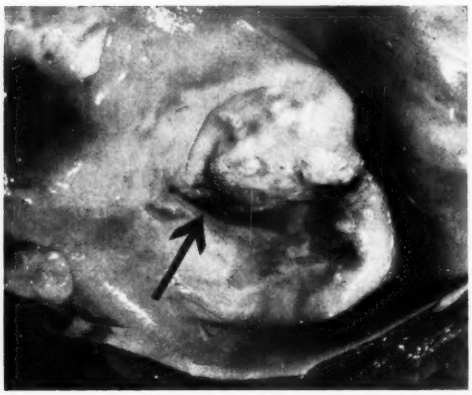

Fig. 1. Mitral valve 14 months after commissurotomy.

regarded and are significant indices of the functional integrity of the valve. The patients (Table III, Cases 4 and 5) whose valves have been both fractured and cut have been most satisfactory, and it has become our routine at present to fracture and then cut the commissure by means of a Bailey knife if necessary.

Our overall surgical experience is summarized in Table IV, which shows a general correlation in mortality rate, complications, and clinical results to those of other clinics as reported by Bland (3). It is not the aim of this paper to report these in detail, but the postmortem findings in one of these patients sheds light on the question as to whether or not a sectioned commissure will again close under the stress of activity. In November 1949 a commissurotomy, by means of a Bailey knife, was performed on a patient with mitral stenosis, who was found at operation to have a type III calcified valve. His course postoperatively was excellent, and he was improved for 12 months, only to develop a recurrence of the symptoms of mitral stenosis and die 2 months later of an acute coronary occlusion. Figure 1 shows his mitral valve 14 months after commissurotomy with the incision bridged completely.

DISCUSSION

After critical evaluation of this type of surgery, we believe commissurotomy is indicated in: (1) mitral stenotics with severe hemoptysis; as Wolff and Levine have shown, this group has an average life expectancy of 3 years. In our limited experience, these are the patients who usually have a type I valve with the expectancy that the chances of these valves resealing is unlikely; (2) mitral stenotics with types II and III valves who are clinically incapacitated by their disease which is rapidly and repeatedly causing them to be bedridden. Some idea of the type is afforded by preoperative fluoroscopy which we routinely used to identify calcification in the mitral valve; and (3) those mitral stenotics who have had arterial embolization in which auricular appendage amputation is contemplated. Since amputation of the auricular appendage makes re-entry into the left auricle difficult, we believe that valvulotomy should be attempted, if feasible, at that time.

Following commissurotomy or fracture of the stenosed mitral valve there is no question either from our study or those in literature (5) that these patients are temporarily clinically improved. If one depended solely on catheterization studies as an index of improvement, the duration and extent in types II and III valves would in the majority of cases be short and minimal. However, the clinical improvement is so much better even when catheterization studies indicate little or no change that one is led to speculate on the discrepancy between the physiological measurements and the clinical well being of the patient. It is likely that the clinical improvement comes about early after surgical treatment by virtue of the fact that the heart and pulmonary vasculature are afforded a short period of relief, which permits adequate compensation for a period. Following this, the gradual return of the pathological hemodynamics is sufficiently slow so that the patient is better able to compensate for them or at least is less affected by the abnormality. In relation to this discussion it is difficult to evaluate the reasons why one of our postoperative patients (Table I) was able to take a 30 mile bicycle trip without evidence of difficulty with hemodynamics comparable to that of patients whom we have encountered wholly decompensated at bed rest. It can clearly be stated that, with the short period

these patients have been studied, it is not possible to determine the permanency of the adjustments, whatever these may be.

Bland in his excellent review has attempted to substantiate by the pathological findings in Cutler's and Beck's patient and in that of Adam's that the valve leaflets do not heal. However, both of his cases are of tissue excision, while these now presented are incisions, and incisions tend to heal, as illustrated by our case. How long this healing takes to be accomplished will depend upon the pathologic type of valve and probably the degree of approximation of the commissure. The more rigid and motionless the leaflet is, the more opportunity it has to seal, and conversely, if the valve is pliable and can move postoperatively, its chances of sealing are considerably reduced.

In conclusion, the period and the extent of clinical improvement are sufficient to warrant further study and to lend encouragement to the continuation of this type of surgery.

SUMMARY

1. This represents a study of 30 patients who have undergone mitral valve surgery, 9 of whom have had careful physiological studies up to 10 months postoperatively.

2. The mitral valve has pathologically been divided into 3 types and these correlated with hemodynamic changes preoperatively and postoperatively.

3. The comparison between the clinical improvement and the hemodynamic changes does not show good correlation. The clinical course of these patients generally shows improvement although a study of the hemodynamics does not indicate any comparable change.

4. Following commissurotomy or finger fracture, cardiac catheterization studies seem to indicate that type I valves do not reseal their commissures, while some of types II and III valves do.

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THE EFFECT OF INCREASING TENSIONS ON THE GROWTH OF EPIPHYSEAL BONE

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FEW factual data are to be found in the literature concerning the effect of tension on the growth of bone, although a good deal has been implied about this subject. It was demonstrated by Haas (3) in 1945 that the longitudinal growth of bone in the distal femur and the other epiphyses in dogs could be arrested by mechanical obstruction. In an attempt to stimulate the growth of long bones in the dog Haas used wires of dissimilar metals to produce an electric current across the epiphyseal line. The wires were looped through the epiphysis and adjacent diaphysis and as growth progressed a mechanical obstruction also developed that stopped the growth of bone. Lane in 1905 had caused a similar arrest of growth while fixing a fracture of the distal end of the femur in a growing boy by placing some staples across the epiphyseal line medially; this resulted in a bowleg deformity as growth progressed. Lane apparently did not appreciate the significance of this finding and did not follow the investigation further. Haas (4, 5) has further stated that if the mechanical obstruction is removed after growth has been arrested for a period of time, the epiphyseal plate is found to be viable and growth is again resumed, but the rate and amount of growth were not definitely established. Blount and associates (1, 2) have made extensive application of this principle in the arrest of bone growth in children for the purpose of equalizing leg lengths. In his extensive investigation Blount has stated that the force exerted by bone growth is relatively great and is sufficient to bend and eventually break one steel staple of $3^3/_{32}$ inch in diameter on each side; if two such staples are used on each side they will bend but rarely break; and if three staples are used on each side the growth of bone will be arrested. Blount and co-workers (2) have further stated that it takes about 900 pounds to break a staple under direct pull; however, when inserted into a living bone the staple bends before breaking and this alters breaking force materially.

The present investigation has been directed toward the determination of the force exerted by the growth of epiphyseal bone and more particularly the rate of growth of bone under increasing tensions. The behavior of cancellous and cortical bone which is in direct contact and under high compression forces with stainless steel pins or other appliances has been noted and certain observed facts are recorded in this article. This study has now been in progress for nearly 3 years and to date 8 calves have been used in the series of experiments.

Holstein calves were selected as experimental animals in this investigation for several important reasons. A new born Holstein calf weighs about 100 pounds and at the time of these operations it weighed about 150 pounds. Their large size and rapidity of growth make them an ideal animal for the insertion of precise mechanical appliances and accurate growth measurements. These animals were of a pure breed and their growth characteristics uniform and well known. A point of great importance is the fact that bovine animals do not possess a fibula and the upper tibial epiphysis becomes an isolated unit, readily accessible and of adequate size for the insertion of suitable mechanical devices. Of further note, the capsule of the knee joint does not extend downward over the tibial epiphysis in the same manner that it projects upward around the distal end of the femur.

The method used in this investigation employed a tension device strung between the proximal epiphysis and the diaphysis of the

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tibia. As growth progressed the device was elongated and the apparatus so constructed that elongation increased the tension. As the tension was increased, the epiphyseal plate was placed under an increasing force. Eventually the mechanical and growth forces became equalized. An equilibrium was established and at this point the growth of bone theoretically ceased.

FORCE MEASURING DEVICES

1. The first type of apparatus used is shown in Figure 1; it consists of a heavy steel coil spring encased in a stainless steel cylinder. The upper and lower ends of the cylinder are tightly closed by stainless steel plugs screwed into position. There is a hole in the top plug just large enough to allow the hooked rod to pass through freely and two tiny holes in the lower plug admitting the retaining wires. A washer and small nut are attached to the bottom of the rod inside the cylinder; the interior is liberally greased with vaseline allowing freedom of motion within the cylinder and protecting the steel spring from rusting. The entire mechanism is nearly watertight when inserted. A heavy pin is then inserted through the epiphysis and the rods are hooked through holes in this pin as shown while a shorter but sturdy pin is driven through the midshaft of the tibia. The lower end of the cylinders are anchored to this diaphyseal pin via heavy wires, threaded double, through holes in the pin. The whole apparatus is placed next to the tibial bone as deeply as possible. Readings are made at regular intervals by relatively high voltage x-rays that penetrate the stainless steel cylinders and show the increasing compression of the springs in the cylinder. The springs used were constructed to specification, giving 1 inch deflection, with a total force of 60 pounds. The limits of the apparatus as read on the compressing springs is therefore 120 pounds (60 pounds on each side). All exposed parts of the spring tension device were constructed of stainless steel, type 316, and no significant reaction to adjacent soft tissues was noted. No observable erosion of the stainless steel parts was ever detected when they were removed. The coil springs within the cylinder were also in a good stage of preservation and had lost little, if any, of their strength.

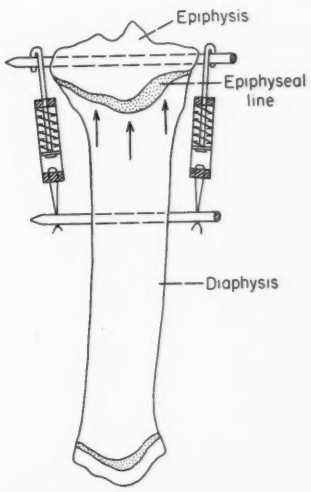
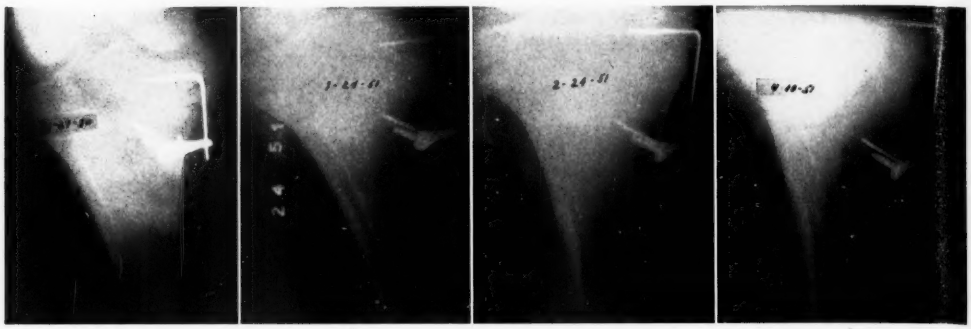


Fig. 1. This diagram shows the spring tension apparatus inserted into the animal. The spring tension devices are strung between the epiphysis and diaphysis. As growth progresses the tension is increased until an equilibrium is established with the growth force equalling the mechanical tension. At this point growth of bone theoretically ceases.

Later in this discussion it will be shown that the force exerted by the growing bone exceeded several hundred pounds and it was found then that at this level spring tension devices were no longer practical.

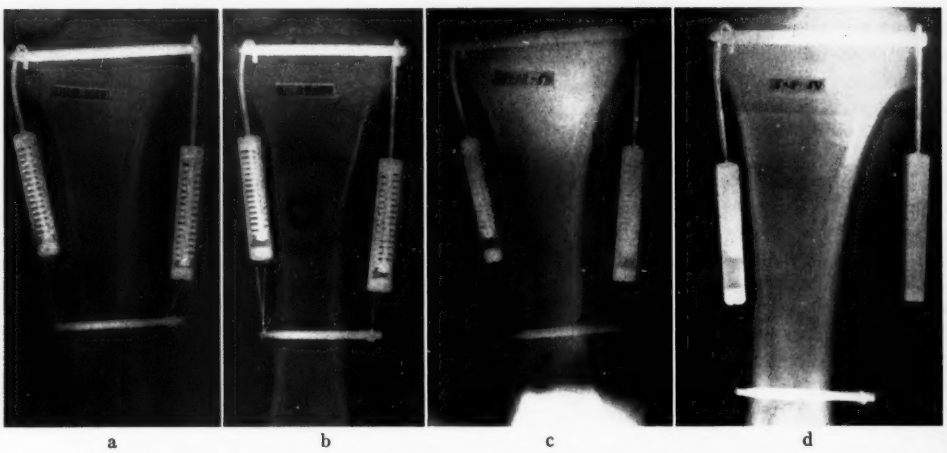
2. The next apparatus used in this study employed the stress-strain relationship of stainless steel wires. When force is applied to a wire, the wire will stretch. The behavior of metals in this respect is conventionally expressed by Young's modulus which is defined by the equation M equals Fl/sA. F is the force applied, l is the length of the wire, s is the resulting stretch and A the cross-sectional area. Young's modulus is a constant, however, only for relatively small elongations. When, as in the present investigation, the wire was stretched far beyond the elastic limit and indeed up to the breaking point, Young's modulus changes materially from its initial value and was therefore not useful.

However, a force elongation relationship for a wire of given dimensions and composition can be determined experimentally up to the



a b c d

Fig. 2. The slider type growth measuring device shown was used on the contralateral side giving normal growth under physiological conditions. The fine wire can be seen to pull upward gradually with the growth of bone at the epiphyseal line. This method gives an accurate measure of growth sensitive to 1/25 inch or 1 millimeter. It was found both simple and satisfactory.



a b c d

Fig. 3. The apparatus used in Animal 1 as it functions within the animal. a, The baseline with some residual slack in the wires and the springs completely filling the cylinders; b, a definite gap appearing under the springs as they are gradually compressed; c, considerably greater compression; d, one of the anchoring wires has broken but the other side continues to function with the spring tension apparatus now nearly locked.

breaking point, and this calibration curve (Fig. 6) can then be used to evaluate an unknown force from the measured elongation. This method has been used in the latter part of this investigation where the force has been so great that spring tension devices are no longer practical.

When a wire of the type and size used in this work has been stretched by an increasing force until the breaking point is reached the accompanying curve shows what happens. The wire used in this series of experiments was of molybdenum stainless steel, well tolerated in the tissues. The initial diameter of the wire was 0.028 inch and it had a breaking strength of 70 pounds; at the breaking point the wire has a final diameter of 0.023 inch and has stretched about 40 per cent of its initial length. It will be seen that a strong initial force is necessary to produce a unit increment of length; however, as the wire is stretched beyond the yield point the additional force

that is necessary to produce the same increment becomes progressively less until the breaking point is reached. By using multiple parallel strands a very large force can be measured, the same curve holding true in direct proportion to the number of strands used. Thus a battery of four parallel strands has a total breaking point of 280 pounds. The identical curve is maintained as for one strand even though the force factor is four times as great. This method gives an accurate measure of force exerted against the wires being stretched, and inasmuch as a relatively great increase in length occurs as the breaking point is approached a sharp end-point is attained. Measurements can therefore be made with a relatively high degree of accuracy.

3. A growth measuring device found to be both simple and satisfactory was placed on the contralateral side in each animal case. The slider type apparatus consists of a thin rod bent at right angles with the short side inserted into the epiphysis and the long arm extending downward. The lower end rides through a small hole in a plate attached to the upper shaft of the tibia. As growth progresses the rod slides upward and the protruding end gives an accurate measure of growth. If, as shown in Figures 2, c, d, the lower end eventually is drawn upward beyond the plate, the distance from its tip to the plate can be readily measured. This type apparatus is shown functioning in Figures 2, a, b, c, d. It accurately shows a growth increment of as little as $1/25$ inch (1 mm.).

EXPERIMENTS

It would be superfluous to give a detailed account of each test but 3 such cases will be presented chronologically as this work progressed.

ANIMAL 1. A 6 weeks old bull Holstein calf was operated upon on February 1, 1950. The spring tension was started at zero pounds across the epiphyseal line and the course of this experiment is shown in Figures 3, a, b, c, d. Roentgenograms were taken at regular intervals and it is to be observed that the coil springs became gradually compressed showing that the force across the epiphyseal line was gradually increasing. At the end of 8 weeks the force exerted had attained 75 pounds which would be about 10 pounds per square inch cross section.

Fig. 4. The final roentgenogram in Animal 2 six months after insertion of the apparatus. The lengths of the tibias have remained exactly the same throughout the test in spite of the gradually increasing tension on one side to 280 pounds. There has likewise been no change in rate of growth after release of this very high force.

The cross-sectional area of the epiphysis of the tibia is about 7 square inches in the animal used. At this time a retaining wire broke on one side releasing the tension on that side. However, the animal was followed for another month during which time the tension on the effective or unbroken side increased from 37 to 52 pounds. It is of interest that the rate of growth on the tension side continued unchanged during the entire test *and at practically the same rate as on the contralateral side.* The graph showing the growth curve under increasing tension accurately fits a straight line (Fig. 7).

ANIMAL 2. A 6 weeks old Holstein calf was operated upon on November 21, 1950. In this case the apparatus used was essentially the same as in that previously discussed. However, taking advantage of the force attained on the previous test the initial force was set at 65 pounds by compressing the springs to the required degree. On the contralateral side the growth measuring device shown in Figure 2 was used.

The limiting value of the coil springs was 60 pounds on each side or a total of 120 pounds and when the 120 pound level was attained—after a period of about 3 months—the apparatus locked. Cessation of growth, however, did not occur and the two stainless steel anchoring wires on each side which had been carefully anchored, without any kinks, finally stretched and broke almost simultaneously; first on one side and then on the other. The breaking strength of these four wires had been previously carefully determined and found to be 70 pounds per strand. Thus, although the limits of the spring tension was 120 pounds at which point the apparatus locked and therefore failed to register, the growth at the epiphyseal plate area continued

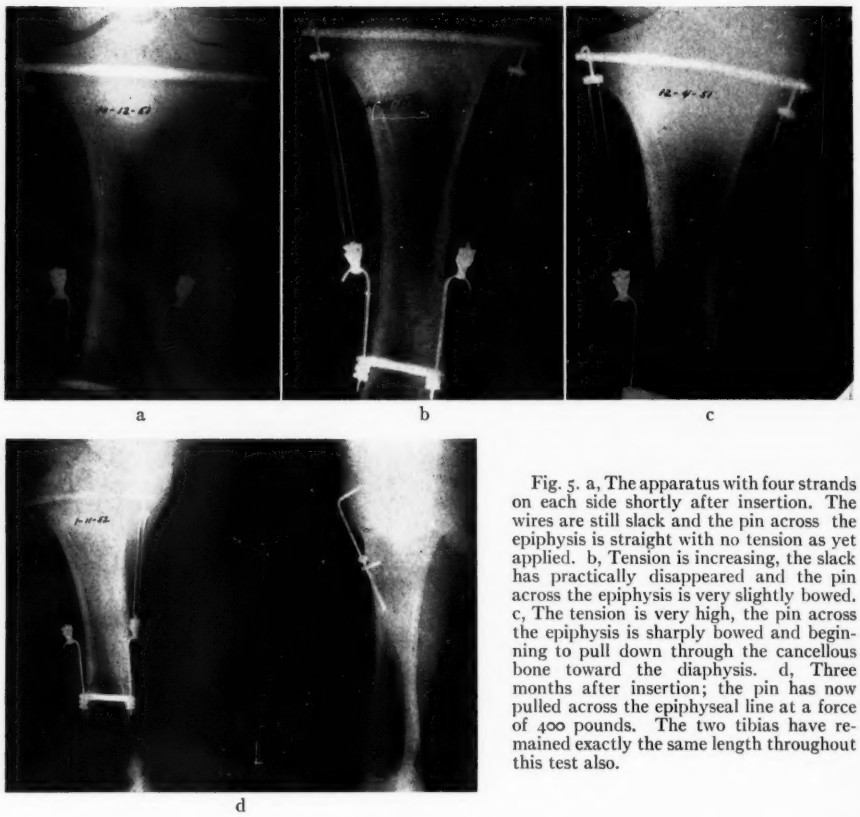


Fig. 5. a, The apparatus with four strands on each side shortly after insertion. The wires are still slack and the pin across the epiphysis is straight with no tension as yet applied. b, Tension is increasing, the slack has practically disappeared and the pin across the epiphysis is very slightly bowed. c, The tension is very high, the pin across the epiphysis is sharply bowed and beginning to pull down through the cancellous bone toward the diaphysis. d, Three months after insertion; the pin has now pulled across the epiphyseal line at a force of 400 pounds. The two tibias have remained exactly the same length throughout this test also.

even up to 280 pounds of wire tension. At this point the wires broke but the epiphyseal growth continued unabated. This entire test lasted for a period of 5 months, taking 2 additional months to stretch and break the retaining wires after the coil springs had become fully compressed and locked.

As noted in Animal 1, growth on the tension side fitted a straight line precisely and was at the same rate and total amount as on the contralateral side. After the retaining wires had broken on both sides the apparatus was removed and a growth measuring device was inserted as on the tension side. This animal was followed for more than another month and during this period of time the rate of growth was identical on both sides showing that the rate was in *no way altered after the release of tension* (Fig. 7). Figure 4 shows the two tibias taken on the same x-ray film with the animal in a standing position and the knees fully extended. It is to be noted that the two tibias have ended up exactly the same length after the period of 6 months that it took to complete this test.

Animal 3. An 8 week old Holstein calf was operated upon on October 11, 1951. In this case the stress-elongation relationship of stainless steel wires was employed because, as seen before, the spring tension devices were impractical beyond forces of several hundred pounds. In this test four strands of wire, 0.028 inch in diameter, were used on each side giving a total breaking strength of 560 pounds. The stainless steel pin through the epiphysis was 0.210 inch in diameter and that through the midshaft was 0.190 inch in diameter. Figures 5, a, b, c, d show the progress of this test. It will be seen that the slack in the wires was gradually taken up by growth of the bone, and eventually the heavy pin gradually pulled

down through the epiphysis and across the epiphyseal line into the diaphysis. The wires did not break but elongated to a point corresponding to a force of approximately 400 pounds.

It is important to note that in spite of this very great force (400 lbs.) the tibia had grown at the same rate and amount as on the control side. Figure 5d shows the two tibias taken on the same x-ray film after a period of 4 months from the beginning of the test. Again the growth curve falls precisely along a straight line. There had been *no slowing of growth* with this very high force which now exceeded the weight of the animal! There has now become established an equilibrium between the force read on the stress-elongation apparatus and the pressure necrosis point of the cancellous bone in the epiphysis. It is of note that very high compression forces have been developed under the pin placed in the epiphysis and under the pin in the midshaft of the tibia. The pin across the epiphysis was in contact with the bone a length of approximately 4 inches and had a cross section of 0.210 inch; this resulted in a cross-sectional contact area of 0.84 inch or 475 pounds to the square inch. The pin across the midshaft of the tibia was in contact only with the relatively thin cortex on each side of approximately 3/8 inch and had a cross section of 0.190 inch. As determined by the method described this yielded a contact pressure of approximately 2,500 pounds per square. There could be observed a moderate overgrowth of bone at the contact sites but no evidence of pressure necrosis by roentgenographic examination.

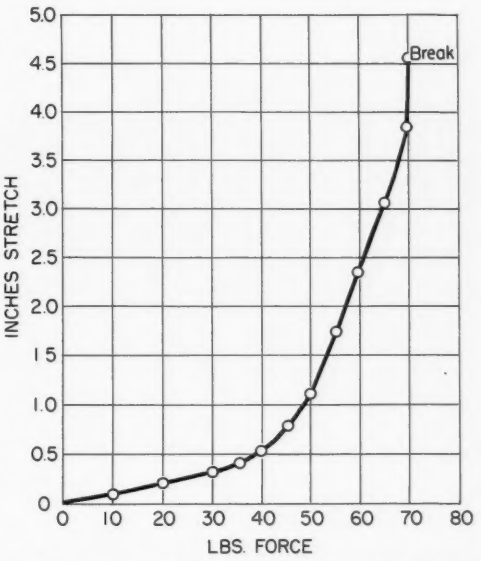


Fig. 6. This graph shows the stress-elongation relationship of a single strand of stainless steel wire with an initial length of 10 inches. The first part of the curve is essentially a straight line and is consistent with Young's modulus, but at the yield point the curve turns rather sharply and each additional unit of force results in a progressively greater increment of length to the breaking point.

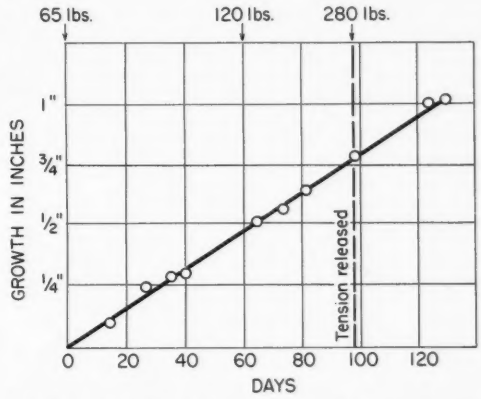


Fig. 7. This graph shows the growth of bone plotted against time; it fits a straight line very precisely. All the cases fit this line exactly from the initial reading of zero pounds to the maximum attained of 400 pounds, the force values alone would have to be changed to fit each case. The graph is of Animal 2 with readings begun when the slack had been eliminated and an initial reading of 65 pounds established. Note that the rate does not change after the high tension had been released.

OBSERVATIONS

The data presented lead to a number of conclusions and points of interest.

1. The rate of growth of bone up to 400 pounds, or 60 pounds per square inch cross section, is exactly the same as on the contralateral side which is growing under normal physiological tensions. In short, the bone on the tension side grew at exactly the same rate and the same amount as the control side.

2. The force attained to date is well beyond any that would be expected from physiological forces such as muscle pull or the weight of the

animal. The force of 400 pounds exceeds the weight of the animal at the time the reading was made. This indicates that the calf could have remained standing on one leg all of the time and that leg would have grown as rapidly as the others. It rather conclusively shows that growth takes place as rapidly when the animal is grazing as when it is lying down at night.

3. It is of further note that the rate of growth of this bone was in no way altered when the epiphyseal plate was released from a prolonged force, up to 280 pounds, which gradually had been increasing over a period of several months.

4. There has likewise been no measurable effect produced by burying a relatively large stainless steel apparatus in the soft tissues next to the bone. There was some overgrowth of fibrous tissues but in general the operation was not excessively traumatic and the stainless steel apparatus did not produce significant reaction.

5. The compression forces that were developed under the stainless steel pins in these experiments were surprisingly high. In the latest test a compression force of 475 pounds to the square inch was developed under the pin in the epiphysis and 2,500 pounds per square inch in the midshaft. At 475 pounds per square inch the heavy pin gradually pulled down through the epiphysis and there resulted an equilibrium between the force as measured on the tension device and the pressure necrosis point of the cancellous bone of the epiphysis. At 2,500 pounds per square inch at the midshaft of the tibia there could be observed an overgrowth of bone about the pin but no evidence of pressure necrosis by x-ray examination.

6. The growth of the tibia under tension up to 400 pounds is a straight line and is identical with the contralateral side under normal or physiological tensions.

ADDENDUM.—Subsequent to the writing of the above manuscript the following additional data have been obtained. The apparatus was modified by replacing the heavy single pin through the epiphysis with multiple screws proximal and distal to the epiphyseal line; multiple wires of the above size and type were strung across the epiphyseal plate connecting the screws.

An 8 month old Holstein was operated upon March 7, 1952, and an apparatus capable of measuring 1,120 pounds was inserted. As soon as the slack was removed, growth promptly and completely ceased. The animal was sacrificed the early part of July 1952 (4 months later), and force readings were made. Because of the heavy caliber of the apparatus, far exceeding the growth force, precise measurements could not be made but a reading of approximately 500 pounds was obtained. This value was a little greater than the weight of the animal.

On May 26, 1952 a similar apparatus capable of measuring 560 pounds was inserted in a 6 week old Holstein. Cessation of growth was again accomplished when the slack was removed, but this animal has not been followed sufficiently long to warrant a final reading. The investigation is being continued to determine more precisely growth force and other related data.

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SURGICAL TREATMENT OF INTRACRANIAL ANEURYSM

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SUBARACHNOID hemorrhage from ruptured intracranial aneurysm is a relatively common cause of death in young or middle aged individuals. Statistically it has been shown that the mortality rate may attain 60 per cent with what has been euphemistically called conservative treatment. Actually "conservative" management is no treatment at all, but relies upon the often futile hope for a spontaneous cure. With such an ominous outlook, early and accurate diagnosis of intracranial aneurysm is a matter of real urgency and effective treatment a vital challenge.

Several larger series of surgically treated aneurysms have been reported, yet many pertinent problems remain unsolved or controversial. We wish, therefore, to introduce our experiences with a series of 73 cases[1] treated during the period 1941 to 1951. Sixty-two cases were observed at the University of Michigan Hospital and 11 additional cases treated by one of us in Grand Rapids.

DIAGNOSIS

Rational therapy of intracranial aneurysm must be based upon a precise diagnosis: location and size of the lesion, presence (or absence) of subarachnoid, subdural, or intracerebral hemorrhage must be known. Such anatomic data should be supplemented by physiologic information concerning the cerebral circulation, with particular reference to competency of the circle of Willis.

Repeated neurologic examinations may disclose evidence of subarachnoid hemorrhage only, without reliable localizing signs; this is notably true with small aneurysms of the anterior part of the circle of Willis. On the other hand, large aneurysms or those with massive surrounding clot usually reveal their location by characteristic focal signs.

Some clue concerning the side involved is afforded by lateralized headache during the period of initial bleeding or by focal or unilateral disturbances in the electroencephalogram. Spinal fluid examination will determine the presence of fresh or old bleeding.

Of all diagnostic measures, cerebral angiography is by far the most accurate and reliable method. Revealing the "anatomy in vivo," it should always be used when aneurysm is suspected.

In this series, angiography was performed in all but 1 case.

More recently, closed (percutaneous) angiography with diodrast has become the method of choice, but the original technique of injecting the contrast medium into the surgically exposed artery still retains its place. In fact, the open method may be more practical when ligation is planned immediately following angiographic study.

In cases of acute subarachnoid bleeding, angiography is preferably carried out under general anesthesia since unnecessary straining or excitement are to be avoided. Intravenous sodium pentothal anesthesia with intratracheal intubation is the technique of choice.

Diodrast may be used in relatively large quantities, yet serious damage may result when many injections are made in rapid succession into the same vessel. Single arteriograms in lateral and anteroposterior projections are essential whereas stereoscopic and special projections add, as a rule, little information. The importance of bilateral angiography must be emphasized, especially in cases without localizing signs; moreover, this technique may reveal multiple aneu-

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[1]Only aneurysms of the carotid system are discussed in this paper.

rysms. Bilateral demonstration of the carotid circulation is accomplished by compression of the contralateral carotid artery during injection, a maneuver which also permits one to reduce the total amount of contrast medium. Concern that angiography may precipitate a new blowout of the aneurysm appears unfounded; therefore, one need not hesitate to perform this test during or shortly after the onset of acute bleeding.

The introduction of contrast media into a diseased arterial system may produce neurocirculatory complications.[1] Untoward reactions, such as convulsions, hemiparesis, and aphasia, are usually of a transient nature. The risk factor with angiography per se appears no greater for aneurysm than for other brain lesions.

Even with perfect technique, an aneurysm may not be demonstrated; e.g. in 4 of our cases it was verified surgically but not shown by angiography. Moreover, the roentgenogram does not always disclose the true size of the lesion. The aneurysm may appear smaller when partially occluded by clot or larger when a covered perforation produces a secondary outpouching.

It is of prognostic and therapeutic importance to recognize other vascular changes such as local vasospasm, arteriosclerotic changes, and displacement of arteries by cerebral swelling or clot in the vicinity of the aneurysm.

Angiography affords physiologic information as to the competency of cerebral blood flow. Bilateral visualization of the carotid systems by unilateral injection indicates adequate circulation through the anterior cerebral and anterior communicant arteries.

The Matas test (2), which formerly was routinely used to determine the competency of the willisian circle, is not reliable; when this test is positive, i.e. when carotid compression is not tolerated, extreme caution must be exercised in permanent ligation. Sweet and Bennett's method of directly measuring blood pressure in the *extracranial portion* of the internal carotid artery is informative, but requires complicated apparatus and does not necessarily give accurate data concerning the blood flow of the diseased *intracranial portion* of the carotid system.

[1]In 1 instance thorotrast caused aphasia and hemiparesis of 3 hours' duration; diodrast caused increase of pre-existing hemiparesis in 1 case and aphasia and hemiparesis lasting for several weeks in another.

GENERAL CONSIDERATIONS

Not all angiographically verified aneurysms are amenable to surgical treatment; those encountered in elderly patients with advanced arteriosclerosis and hypertension are better left alone. Ideally, surgical treatment must achieve complete elimination of the aneurysm from the cerebral circulation. This objective can be attained by direct intracranial attack; either the neck of the aneurysm is ligated or the vascular segment containing the aneurysm is "trapped" between ligatures. Unfortunately, the intracranial approach is frequently unsafe, because it may seriously endanger cerebral circulation.

There is, however, a therapeutic alternative exemplified by cervical ligation of the carotid artery. This procedure reduces the cerebral blood flow and the head of pressure within the aneurysm, thus promoting thrombosis and spontaneous healing.

The method of management must be strictly individualized. It depends primarily upon the location of the lesion with reference to the dominant hemisphere.

An equally important factor is timing of the operation. It matters little whether angiography is performed during the acute or quiescent phase, but the risk of intracranial surgery is markedly increased during the period of acute bleeding. The same considerations apply to cervical ligation to a lesser extent, yet patients with repeated minor hemorrhages may be so improved that subsequent intracranial ligation may be carried out with less risk or this step may prove unnecessary.

Cervical ligation. Cervical ligation of the carotid artery must be done under local anesthesia; the conscious patient should be observed for additional neurologic signs and symptoms (hemiparesis, aphasia) for at least 1 hour before the definitive ligature is applied. In this series, cervical carotid ligation was the only treatment in 29 patients.

The internal carotid artery was totally occluded in 18 cases, partially occluded in 3 cases; two stage total ligation of internal carotid artery was done in 4 cases, ligation of the common carotid artery in 2 cases, combined common and external carotid ligation in 1 case, and Selverstone clamp in 1 case. The problem as to whether the internal or the common carotid artery should be ligated still remains controversial. Two stage ligation, first of the common, later of the external carotid artery has obvious value. Various types of ligature such as silk, kidney tape, silk over fascia, and tantalum clips were used, without appreciable difference in results. The Selverstone clamp was applied in 1 case.

Cervical ligation immediately increased a pre-existing hemiparesis in 2 cases; however, the ligature was not removed. One of these patients died subsequently (the only mortality after cervical ligation), the other made a slow but eventually complete recovery. In 12 additional patients hemiparesis developed from 2 hours to 10 days postoperatively. In this group, 8 cases ultimately cleared completely and only 4 remained permanently hemiparetic.

Briefly then, the mortality rate of cervical ligation was 3.4 per cent but the incidence of hemiparesis was 41.4 per cent. There was no definite correlation between the patient's age and the incidence of hemiparesis.

Intracranial ligation. Intracranial operation alone was performed in 25 patients with a mortality of 10 (40 per cent). Unilateral frontal osteoplastic craniotomy, similar to the pituitary approach, was used. Exposure of the surgical field is facilitated by draining spinal fluid through an inlying lumbar puncture needle and by hyperextended position of the head. Thus, the frontal lobe is easily retracted, lessening the risk of rupture of the aneurysm. In the presence of brain swelling or intracerebral clot, resection of the frontal (or temporal) pole may become necessary. As a safeguard against uncontrollable bleeding, the ipsilateral or both carotid arteries may be exposed in the neck prior to craniotomy and surrounded by a loose ligature which can be tightened in case of emergency. Rupture of the aneurysm during exposure occurred in 12 cases. Recent technical refinements promise to make the intracranial approach safer, e.g. the use of autonomic blocking agents (hexamethonium bromide) during operation may assure controlled arterial hypotension with pronounced fall of pulse pressure. With the arteries partially collapsed and hardly pulsating, operative hemorrhage is strikingly reduced, hence, the danger of rupturing the aneurysm during manipulation is lessened. A valid objection to this method is the increased danger of cerebral circulatory insufficiency which threatens patients with artificially induced hypotension after ligation.

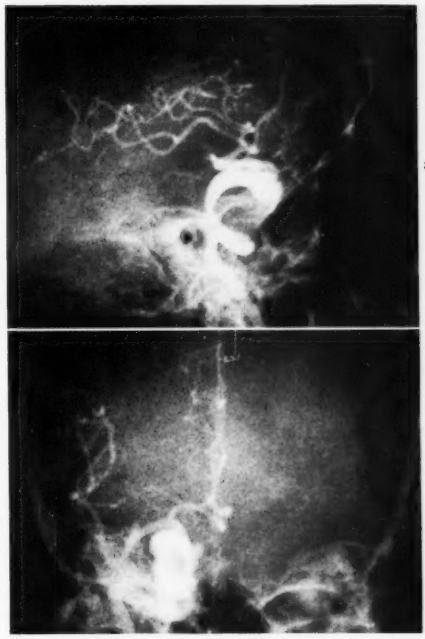

Fig. 1. a, Large subclinoid aneurysm of internal carotid artery with clot outlined by contrast medium in lumen of aneurysmal sac (lateral view). b, Frontal view of arteriogram of above aneurysm.

Ten of the surviving 15 patients developed hemiparesis (66.6 per cent) which was transient in 9 survivors (60 per cent).

Cervical and intracranial ligation (trapping). Eighteen patients had combined cervical and

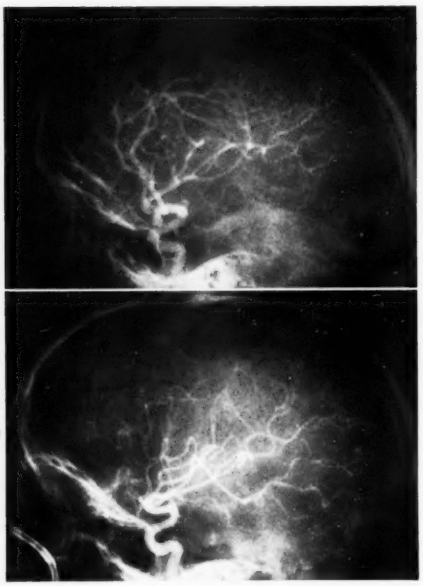

Fig. 2. a, Lateral view of arteriogram demonstrating aneurysm of anterior communicating artery with filling of distal portion of both anterior cerebral arteries by contrast medium. b, Injection of opposite carotid artery showing nonfilling of anterior cerebral artery.

intracranial ligations. In 13 cases the interval between both procedures was from 2 days to 13 months during which time hemiparesis occurred in 8. It is worthy of mention that 4 of the 8 patients who developed neurologic complications following cervical ligation died shortly after the intracranial operation.

The overall mortality of the combined cervical and intracranial ligation was 9 cases (50 per cent) with permanent hemiparesis in 2 survivors (22 per cent).

MANAGEMENT OF ANEURYSMS IN SPECIAL LOCATIONS

Subclinoid carotid aneurysm. These usually large lesions, also known as parasellar aneurysms, produce symptoms mainly by their expansile character, but due to their protective dural covering they are less likely to rupture. The problem here is not so much that of saving the patient's life, but to relieve severe trigeminal pain and to restore or preserve vision and eye movements. Cervical ligation of the carotid artery is the treatment of choice.

Such conservative approach appears to be the more warranted as subclinoid carotid aneurysm frequently affects elderly hypertensive or arteriosclerotic patients and tends to heal spontaneously by thrombosis and calcification (Fig. 1).

Of 8 cases, 4 had cervical ligation with 1 fatality (25 per cent). Four others had combined cervical and intracranial ligation with 2 deaths (50 per cent). This high rate of mortality indicates that individuals with general cardiovascular disease do not tolerate interference with the cerebral circulation.

Supraclinoid aneurysm of the carotid artery. This group, comprising 32 cases, represents the most common type of intracranial aneurysm in this series. Supraclinoid aneurysm arises either proximally from the intradural segment of the internal carotid artery expanding medially against the optic nerve or chiasm, or from the distal intradural portion near or at the origin of the posterior communicating artery and compresses the third nerve by posterolateral extension.

Judged from the arteriographic picture, supraclinoid aneurysms seem to be ideally suited for intracranial attack, specifically for ligation of the aneurysmal neck. This desirable goal cannot always be safely attained for several technical reasons since the neck of the aneurysm is usually concealed behind the carotid artery and hence not readily accessible, also this portion of the lesion is usually its weakest point, rupturing upon attempted exposure for ligation. Some of the developmental aneurysms possess a strong-walled stalk which may be ligated with impunity. In the presence of marked arteriosclerotic changes, it appears wiser to trap the aneurysm rather than to risk rupture. Inclusion of the posterior communicating artery in the trapped vascular segment may then be unavoidable and thus further reduce the collateral blood flow to the hemisphere, yet if this vessel is an important tributary of the aneurysm, it must be ligated.

Among 32 treated cases there were 7 deaths (22 per cent), 11 patients became

hemiparetic (34 per cent), but the neurologic damage remained permanent in only 3 patients (9.4 per cent). If the figures are broken down according to procedure, cervical ligation was done in 15 cases without fatality but with 7 instances of supervening hemiparesis (46 per cent). After 6 intracranial ligations 3 deaths occurred (50 per cent) and transient hemiparesis occurred in 1 surviving patient. Eleven cases of combined cervical-intracranial ligation had a mortality of 4 (36 per cent) and 2 instances of temporary hemiparesis.

Aneurysm at the internal carotid bifurcation. Four cases of this type were encountered. One patient was subjected to intracranial intervention because it was thought possible to clip the aneurysmal stalk without impeding circulation in the anterior and middle cerebral arteries, but the attempt was fatal. It would probably have been safer to reinforce the thin wall of the aneurysm with muscle tampons. Three additional cases had cervical ligation without a death. Two patients developed a permanent hemiparesis.

Aneurysm of the middle cerebral artery. Aneurysms of the proximal segment of the middle cerebral artery are, as a rule, unsuited for direct ligation since this would result in severe hemiparesis or aphasia, frequently with fatal outcome. In order to promote healing, cervical carotid ligation was used in 2 cases, apparently with success. A remarkable case in evidence that these lesions may occasionally heal spontaneously occurred in this group. A ruptured aneurysm of the middle cerebral artery (demonstrated by angiography) had caused an intracerebral and subdural hematoma with the clinical signs of hemiplegia and aphasia. The subdural clot was removed, but the aneurysm not treated. Surprisingly enough, the patient was alive 9 years later and had recovered from the severe neurologic disability.

In another case, an embolic mycotic aneurysm, associated with subacute bacterial endocarditis, was found when an intracerebral clot was evacuated. Here, intracranial and cervical ligations were required to arrest profuse hemorrhage. Except for residual hemiparesis, this patient is well after 3 years.

a b

Fig. 3. a, Frontal view of arteriogram demonstrating aneurysm of anterior communicating artery with filling of distal portions of both anterior cerebral arteries by contrast medium. b, Injection of opposite carotid artery showing nonfilling of anterior cerebral artery.

Aneurysms of the distal midcerebral branches may be excluded from the circulation by ligation of the involved artery (2 successful cases).

Aneurysm of the anterior cerebral artery. Next to the supraclinoid carotid aneurysms, those of the anterior cerebral artery were most commonly encountered (18 cases). The following subgroups may be distinguished: (1) aneurysms arising from the proximal segment of the anterior cerebral artery between the internal carotid bifurcation and anterior communicant artery (4 cases); (2) aneurysm of or at the anterior communicating artery (13 cases); (3) aneurysm arising from the anterior cerebral artery distal to the anterior communicant vessel (1 case).

Since the anatomy of the anterior cerebral arteries with their connecting link is quite variable, bilateral angiography is essential. In 4 cases of aneurysm at the junction of one anterior cerebral with the anterior communicating artery, the proximal stem of the anterior cerebral artery at the site of the aneurysm supplied *both* distal anterior cerebral branches, whereas the proximal anterior cerebral of the opposite side was hypoplastic and not demonstrable by angiography (Figs. 2 and 3).

Aneurysms of the proximal anterior cerebral artery are suited to intracranial trapping, especially if the communicant vessel is competent. If, however, Heubner's recurrent artery

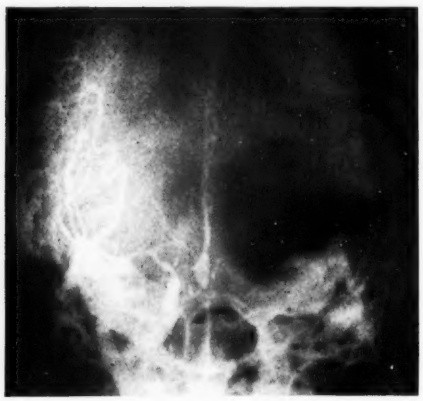

Fig. 4. Aneurysm of anterior communicating artery with arterial spasm of vessels adjacent to lesion (frontal view).

happens to be included in the ligature, hemiparesis is likely to develop due to softening of the anterior limb of the internal capsule. Intracranial trapping was done in 3 cases with 1 permanent hemiplegia.

Cervical ligation of the internal carotid prior to intracranial attack is to be avoided since ligation of the proximal stem of the anterior cerebral artery will shut off important collateral circulation to the middle cerebral artery producing hemiplegia.

The management of aneurysms arising from or at the anterior communicating artery poses a difficult problem. Direct ligation of the neck is rarely possible, trapping may occlude both anterior cerebral vessels. Bilateral ligation of these arteries is not necessarily fatal, but is likely to produce profound mental deterioration and tetraparesis. Two patients in our series died, 9 and 11 days respectively, after bilateral anterior cerebral ligation. If, therefore, both distal anterior cerebral arteries spring from the aneurysm, local ligation would be disastrous. Such difficulties may be overcome either by partial cervical carotid ligation on the more involved side or by wrapping of the exposed aneurysm with muscle. The first technique (common carotid ligation) was utilized in 2 patients with immediate subsidence of recurrent subarachnoid bleeding; but, so far, the postoperative period has not been long enough for final evaluation.

Obviously, cervical ligation has little to offer when the aneurysm of the anterior communicant artery is equally supplied from both anterior cerebral arteries. In a case of this type, the aneurysm, which was situated at the junction of the anterior cerebral with the anterior communicating vessel, ruptured before complete intracranial exposure. A series of clips was hurriedly placed on the proximal and distal portions of the anterior cerebral artery, including a part of the aneurysmal sac. Finally muscle was packed around the region. The patient survived with a hemiparesis which eventually cleared completely.

The rare aneurysm of the distal portion of the anterior cerebral artery is treated by ligating the vessel proximal to the lesion without necessarily uncovering the aneurysm itself. Complete exposure requires a parasagittal approach along the falx.

Among the entire group of 18 aneurysms of the anterior cerebral artery there were 6 postoperative deaths (33 per cent), and 8 cases of hemiparesis (44 per cent). Fortunately, hemiparesis in anterior communicating aneurysm proved transient in all (5) cases. It was permanent, however, in 1 case of proximal anterior cerebral aneurysm, presumably due to occlusion of Heubner's artery.

Multiple aneurysm. No general rules can be made for multiple aneurysm as each case presents its individual problem in management. Bilateral angiography is mandatory here. In 1 instance, the patient exhibited the syndrome of a right supraclinoid carotid aneurysm which was successfully treated by cervical ligation. Forty-six months later, he had a subarachnoid hemorrhage from an aneurysm of identical location on the left side. This lesion was approached intracranially with the hope of clipping the neck, but the aneurysm ruptured. In this emergency, the left carotid artery had to be ligated in the neck, leaving the patient dependent upon the inadequate vertebral circulation, with subsequent fatality.

The outcome was more favorable in another patient harboring 2 aneurysms (1); there was one aneurysm of the supraclinoid portion of the right carotid artery and another at the beginning of the right middle cerebral artery.

It was possible to trap the carotid aneurysm and to occlude the neck of the middle cerebral aneurysm. The patient developed hemiplegia, but eventually recovered completely.

In 2 other cases cervical carotid ligation was done with satisfactory results.

DISCUSSION

In evaluating surgical results, rate of mortality and disability from various procedures must be compared. The mortality figures in this series have been approximately 15 times higher for intracranial ligation than for cervical ligation. Early inexperience and improper selection of cases may account for such poor results, but even with stricter indications and greater surgical perfection the risk of intracranial ligation is likely to remain high.

On the other hand, a permanent cure is practically assured when a patient has successfully recovered from intracranial trapping of a solitary aneurysm. The ultimate prognosis with cervical ligation is more doubtful as it gives no absolute guarantee against further bleeding; in fact, 2 of our patients with cervical ligation died later on, outside of the hospital, from what was presumably recurrent hemorrhage. Regardless of its uncertain outlook, we consider cervical carotid ligation as the simplest, least harmful, most effective treatment. At present, it appears to be the method of choice in the management of carotid aneurysm to be followed by intracranial trapping only if symptoms persist or recur. Aneurysms of, or distal to the circle of Willis frequently require intracranial ligation, yet cervical ligation has proved beneficial in special situations.

We may summarize our views by stating that therapeutic restraint for the patient's benefit dictates a conservative approach to the problem so long as such a striking discrepancy prevails in mortality figures for cervical and intracranial ligation. Recent favorable reports indicate, however, that a considerably lower mortality rate for the intracranial procedure may be attained (3).

Postoperative disability, hemiparesis, or aphasia has been high in this series, regardless of the technique employed. It is gratifying to note, that neurologic complications cleared in most cases, leaving no or only minor nondisabling residuals. Hemiparesis seemingly followed more often cervical than intracranial or combined ligations. This difference is more apparent than real since the higher mortality rate of the latter procedures conceals statistically the incidence of postoperative hemiplegia.

Fig. 5. Supraclinoid aneurysm with arterial spasm of vessels adjacent to lesion (frontal view).

The anatomic basis of hemiplegia following carotid ligation has been a matter of considerable controversy. It has been assumed that hemiplegia immediately following carotid ligation was due to ischemic anoxia, and that delayed hemiparesis resulted from thrombosis or thromboembolism. This is frequently verified at autopsy. Schorstein has shown that hemiplegia following carotid ligation is usually caused by microscopic ischemic changes in the cerebral cortex and white matter rather than by gross thrombosis of major arteries.[1]

There can be no doubt that even temporary and functional impairment of the cerebral circulation, such as is associated with vascular

[1]In a recent case of ruptured supraclinoid carotid aneurysm (not included in this study) right hemiplegia and aphasia followed 40 hours postligation of the left common carotid artery, and death ensued 2 days later. At autopsy, the carotid system at and distal to the site of ligature (internal carotid, middle, and anterior cerebral arteries) was free from thrombosis. The left middle cerebral artery was completely surrounded and compressed by clot originating from the adjacent ruptured aneurysm. The bleeding had spread through the left sylvian fissure and diffused throughout the subarachnoid spaces of the frontoparietal cortex.

spasm, may produce the clinical picture of hemiparesis. Marked narrowing of arteries in the neighborhood of the bleeding aneurysm can frequently be recognized on arteriograms (Fig. 4). This may be due to compression of a vascular segment by surrounding clot, local vasospasm, or a combination of both factors. Under such conditions, hemispheral circulation is precariously maintained as the collateral blood flow may be inadequate as well. Any further interference with circulation may then precipitate disastrous ischemic changes in the distal vascular bed of the cortex. Cerebral vasospasm is likely to be enhanced by the procedure of angiography, by operative reduction of blood flow or trauma to the arterial wall incident to cervical carotid ligation.

It should be mentioned that vasospasm may be an important protective mechanism tending to arrest bleeding through reduced local blood flow thus promoting spontaneous healing of the aneurysm. This mechanism probably explains the favorable effect of cervical ligation on some aneurysms distal to the circle of Willis. In other words, vasospasm may be considered a beneficial therapeutic factor that should not be counteracted. Therefore, contrary to generally accepted views the use of vasodilator drugs and sympathetic block may be undesirable or even harmful in cases of bleeding aneurysm.

On the other hand, vasospasm promotes the development of hemiparesis. Frightening as such a complication may be, it suggests that favorable conditions exist for healing of the aneurysm. The possibility for such a neurologic deficit must be accepted as a calculated and necessary risk, inasmuch as there is a reasonable chance of recovery.

Hemiparesis after cervical ligation certainly shows that the cerebral circulation is at least temporarily inadequate. Any previously planned intracranial procedure, therefore, should be postponed, or entirely omitted if time proves it to be unnecessary.

CONCLUSIONS

1. Seventy-three cases of surgically treated aneurysm are reported. These were treated by cervical ligation of the carotid artery in 20 cases, intracranial ligation in 25 cases, and combined cervical ligation of carotid and intracranial ligation in 18 cases.

2. While each case must be considered individually, the following facts stand out. Cervical ligation of the carotid artery has had a low operative mortality (3.4 per cent) with a fairly high incidence of postoperative hemiparesis which, however, has shown a high incidence of functional recovery; further long term observations are necessary to determine how many patients are permanently cured. When cervical ligation is combined with intracranial operation, the operative mortality (50 per cent) is approximately the same as for those cases treated by intracranial ligation alone (40 per cent). Intracranial ligation has the advantage of dealing directly with the lesion and effecting a permanent cure, but with greater risk.

3. Vasospasm in the neighborhood of aneurysm favors healing but predisposes to complication in treatment (hemiparesis).

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EVALUATION OF CYTOLOGIC DIAGNOSIS OF GASTRIC CANCER

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ROENTGENOLOGY is, at the present time, by far the most important technique available for the diagnosis of gastric cancer, and if it is utilized fully it can be expected to yield unequivocable results in a great majority of instances. LaDue and associates, in their study of 1,022 patients with the disease, found that roentgenography was diagnostic 91.5 per cent of the time, without recourse to other diagnostic methods. In an additional 3 per cent of these patients, the roentgenologist's report suggested the possibility of an abnormality, but findings were inconclusive. Maimon and Palmer have described similar findings recently. If gastroscopy is used when the x-ray report is inconclusive or negative, positive diagnosis of more than 95 per cent of all cases of gastric cancer can be anticipated.

In spite of this substantial accomplishment in positive diagnosis, the percentage of 5 year cures achieved by surgery remains small. About 1 patient in 3 is resectable, and recurrence is common. Bell has analyzed 540 cases of gastric carcinoma occurring at the University of California Hospital between 1930 and 1947; of these, only 186 proved to be resectable. Among those resected, only 14 lived 5 years or longer after the operation, and an additional 38 patients were still alive, for shorter periods, at the time of the report. Obviously, although roentgenology permits a high degree of diagnostic accuracy, additional diagnostic techniques are very much needed.

One approach to the problem has been to use roentgenology as a case-finding method to survey that portion of the population which is known to be particularly susceptible to gastric cancer. State, at the University of Minnesota Hospital, made roentgenologic studies of all patients over 50 years old who had (1) a positive family history, (2) achlorhydria or hypochlorhydria, (3) pernicious anemia, (4) reduced hemoglobin values or occult blood in the stool. In a 5 year period, 1,774 patients were examined and 11 silent carcinomas were discovered. The cost per cancer discovered by this method is obviously high, although it is perhaps not prohibitive. Routine x-ray examination would not seem to be the answer, however, to the present need for a screening technique which can be easily applied in private practice and that will be relatively inexpensive.

It is also desirable that a supplementary diagnostic technique be available for use in those instances in which x-ray findings are inconclusive. X-ray is particularly inadequate in those instances in which the chief roentgenologic finding is of polyps or ulcers. Lampert found that, of 550 ulcers believed benign on the basis of x-ray and other clinical studies, no less than 73 were later found to be malignant.

For about 3 years there has been considerable interest in the possibility that cytological techniques might be adaptable to these requirements. The observation and interpretation of exfoliated cells from the stomach has so far proved to be more difficult than the observation of cells from some other body fluids, however, and there remain major obstacles to its wider application in gastric diagnosis. Some time ago this laboratory reported that the use of papain lavage might be, at least in part, a method of overcoming the limitations of gastric cytology; this report is a comparison of the results obtained by the use of papain as contrasted with the standard saline lavage.

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HISTORY

The difficulties inherent in the application of cytological methods to the diagnosis of gastric cancer are apparent in the variety of methods that have been advocated. Graham, Ulfelder, Green, and Meigs (5, 17), for instance, have reported on the results of direct aspiration from a fasting stomach, and also on the use of saline lavage. They found that the latter method was more effective, permitting positive diagnosis in 12 out of 14 cases of gastric cancer, as compared to the 15 positive diagnoses out of 24 cases discovered without lavage. Pollard and associates (3, 4, 11), on the other hand, found that saline washes added little to the accuracy of the diagnosis.

Richardson, Hunter, Bishop and Queen (2, 12, 13) have reported on a technique for embedding sections of gastric aspirations for cytohistological study; they believe that a greater concentration of material is obtained by this means, and that the cellular relationship which is thus preserved is useful. They reported a sensitivity of 66.7 per cent in 27 proved cases.

Seybolt, Papanicolaou, and Cooper have intensively studied the problem of increasing the sensitivity of cytological techniques in the diagnosis of gastric cancer. They found that an accuracy of 60 per cent was achieved by intensive lavage with Ringer's solution, as compared with an overall average of 32.8 per cent. They suggest that prompt handling of aspirated material is more important to accuracy than is sometimes realized.

Those interested in the application of cytology to the diagnosis of gastric lesions are aware that the future usefulness of the technique depends in great part upon the development of more efficient methods of collection and concentrating cells, so that more material is available to the cytologist with greater preservation of morphological detail. One possibility is mechanical irritation of the gastric mucosa; Panico, Papanicolaou, and Cooper have recently reported excellent results with an inflatable abrasive balloon. They were able to make a diagnosis in 11 of 17 proved cases by this method; in only 4 was malignancy demonstrable by routine spread technique.

Another approach to the problem is the search for a chemical stimulant which will induce desquamation without affecting cell structure. Hollander, Hess, and Sober have proposed an emulsion of eugenol in water; in preliminary tests with normal subjects they found that a 2 per cent solution, passed into the stomach after it was emptied by aspiration and left for 15 minutes, greatly increased the amount of cellular material that could subsequently be withdrawn. In our laboratory we have been investigating the results to be obtained with papain solutions, as previously reported (14).

MATERIAL AND SOURCES

This study is based upon 1,000 cases, collected from various sources. The cases collected at the University of California Hospital included both those patients suspected of gastric cancer and those for whom a gastric analysis was requested; the latter group thus included patients with a wide range of complaints. The patients at the other institutions, and those of private physicians, were all suspected of gastric cancer before the cytologic study was undertaken.

These 1,000 cases are roughly divided into two groups. The larger group of 600 patients was studied from 1948 to the early part of 1950; in this group, specimens were obtained by simple aspiration from the fasting stomach, or by saline lavage. The second group, studied from early in 1950 to the present date, is made up of 400 cases in which a papain lavage was utilized. All specimens were examined by the Papanicolaou and Traut procedure. Routine screening was done by specially trained laboratory technicians, but the final diagnosis of suspicious cells was reserved for the pathologist. All cases were followed to a conclusive diagnosis by pathological methods when it was possible; otherwise, it was necessary to accept the clinical diagnosis. Fifty cases, most of them in the saline series, had to be discarded for lack of information.

METHOD

In the earlier series, lavage was carried out, when it was possible, with about 100 cubic centimeters of isotonic saline solution. The

return was centrifuged immediately and smeared, fixed, and stained by the standard methods. Otherwise, a fasting gastric specimen was utilized. Our laboratory failed to find any significant difference in the results obtained by the two methods. This may be explained by the fact that we were not able to control the lavage technique, in all instances, as thoroughly as other investigators.

The papain technique was developed because of our dissatisfaction with the saline lavage method. A study of autopsy and surgical specimens indicated that the "mucous barrier" that normally lines the gastric mucosa was rich in significant cellular content; the search for an agent that would make these cells available for microscopic study ultimately led to the use of papain, as reported earlier (1).

The solution used is made up from a stock isotonic buffered tap water. If the available tap water is too "hard," the *p*H will be too high in spite of the phosphate mixture and distilled water should be employed. To 5 gallons of water are added 750 grams of $Na_2HPO_4.12\ H_2O$ (or the equivalent, depending upon the number of molecules of water of crystallization in the dibasic sodium-acid phosphate obtained) and 0.4 mol of hydrochloric acid (e.g. 400 ml. of 1 N HCl). The resultant *p*H value will be between 7.2 and 7.4, within the normal physiologic range, and the buffering action will delay the acid digestion of cells released from their mucous coating.

An electric mixer has been found to offer great convenience in getting the papain into solution, but grinding the papain to a paste with a small amount of buffer in a mortar will also serve. A convenient routine is to place 3 level teaspoonfuls of papain powder in the blendor, add buffer to cover the blades, and run the stirrer for 3 minutes. Then the rest of 400 milliliters of buffer solution is added and the stirring continued for 2 more minutes. The mixture is then transferred to a closed container and briefly shaken with a heaping teaspoonful of activated charcoal. The latter absorbs fine particles which would otherwise pass through the filter paper. The mixture is then filtered through a thin hard surface paper which allows most rapid filtration without letting particles come through. The first few drops will contain charcoal and these may be returned to the funnel. The filtrate should now be sparkling clear. Any particulate matter will later be recovered in the digest sediment and will obscure and dilute the cells.

The filtrate can be kept under refrigeration for up to 4 days without risk. Since the filtration takes up to 45 minutes, the laboratory personnel must receive adequate prior notice of an order for lavage. The filtration may also be allowed to proceed overnight for an early morning lavage.

Immediately before instillation, approximately 1 gram of cysteine hydrochloric acid is added for activation of the papain. This is easily soluble.

The average stomach will contain about 250 milliliters of liquid without distention, but we have generally instilled 500 milliliters of solution to ensure contact with the whole gastric surface. An ordinary Levin tube may be used. A 3 ounce asepto syringe is more convenient for instillation than a glass syringe, since the syringe must be detached from the tube each time it is necessary to refill it.

Before the solution is instilled, the fasting specimen should be removed and discarded, since it invariably contains a large component of saliva and sputum cells. The instillation may also be carried out after the completion of an ordinary gastric analysis, the tube being left in place.

The solution should be left in the stomach for about 10 minutes, during which time the patient should turn from side to side, occasionally. Usually from 400 to 450 milliliters of the digest are recovered. Rarely, no solution was recovered because of duodenal passage. There has been no harmful effect. The procedure may be repeated the next day to allow time for accumulation of exfoliated cells.

The turbid instillate should be centrifuged within a half hour of its recovery. Two of the missed cases showed complete digestion of the cells because of a greater delay. It is preferable that the entire digest be centrifuged, but because most cases of cancer produce cells in

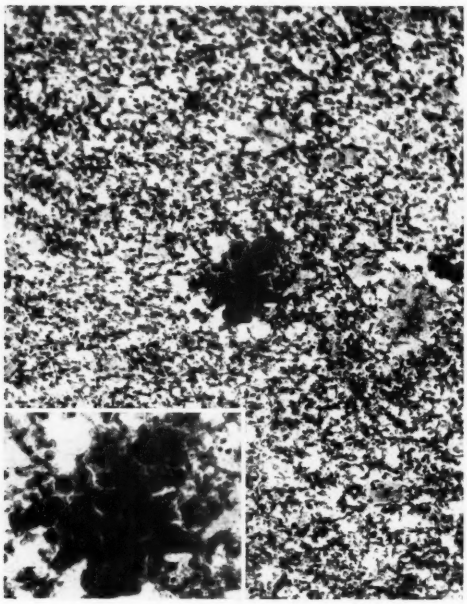

Fig. 1. Papain gastric smear showing a cluster of malignant cells clearly seen in a rich cellular field.

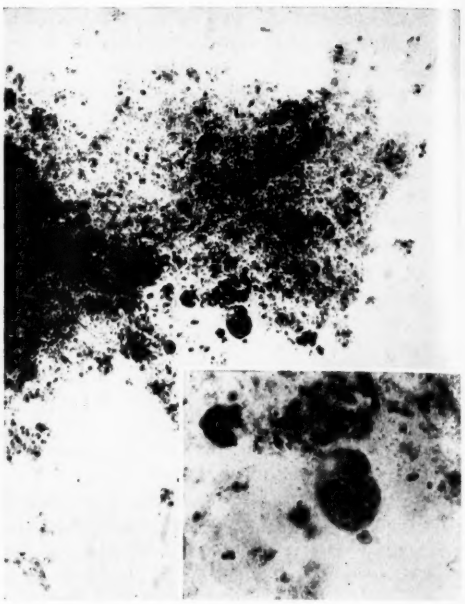

Fig. 2. Saline gastric smear showing a great amount of debris and poorly outlined cells.

great numbers, a well-mixed aliquot will usually permit diagnosis.

As papain is mucolytic, the natural adhesiveness of the gastric material is lost from the specimen. This adhesiveness is most conveniently restored by placing 1 or 2 milliliters of ordinary serum into the bottom of the centrifuge tube. The tube is first filled with digest and the heavier serum injected into the bottom of the tube with a long spinal needle or a needle such as is used to fill a Wintrobe hematocrit tube. The cells will be thrown down into the serum and coated, and will subsequently stick to the slides.

During the digestion of mucus, a fine amorphous precipitate is produced. It has recently been realized that occasional unsatisfactory smears have been caused by inclusion of this precipitate in the cellular sediment. Such inclusion may be prevented in this manner: the digest is centrifuged at slow speed (approximately 500 r.p.m.) for 5 minutes. There will then be a compact cellular layer at the bottom of the tube and a distinct overlying fluffy white portion of precipitate. The fluid is poured off and a small amount of water is poured into the tube, with swirling, to bring the precipitate into suspension. The suspension is then poured off and the tube inverted to drain for several minutes on filter paper. The cells, rendered sticky by the serum, will remain in the tip of the tube as a coherent mass. This can then be removed for smearing with a small cotton swab, wetted with serum.

The cells are smeared on clean dry slides (washed, if new) and immediately placed into fixative (half 95 per cent alcohol, half ether). They may be left in fixative indefinitely, or removed after 20 minutes of fixation and allowed to dry for purposes of transportation. They are stained by the usual Papanicolaou method.

If the sediment is well mixed and not of unusually large quantity, 4 slides from a wash specimen are usually sufficient for a diagnosis. In our experience, an experienced technician can screen 4 such slides in about 30 minutes. The technician marks the location of any sus-

picious material, and the final diagnosis is made by the pathologist.

Undesirable side effects of the papain lavage have been few and inconsiderable. The first few patients to whom the technique was applied were later examined gastroscopically by Doctor M. Dailey of the Department of Medicine; no harmful reaction could be detected by visual means. There is a theoretical risk of dissolving a thrombus in a previously eroded blood vessel and thus occasioning hemorrhage, since papain is a general protein digestant, but we have had no untoward incidents to date. There have been several instances of blood-tinged returns, but in all these patients the bleeding was minor in extent and of short duration. When the patient was known to have suffered massive gastric hemorrhage previously, papain lavage was delayed for a period of 10 days to 2 weeks. In 2 instances, however, such lavage was performed inadvertently on patients who only a few days previously had had severe hematemesis, but fortunately there was no clinical evidence of further hemorrhage due to the papain lavage.

RESULTS

In analyzing both groups of patients, i.e., those with saline lavage and those with papain washing, the standard classification was followed:

I. No malignant cells present.
II. Atypical nonmalignant cells present.
III. Inconclusive cells present, which may be from a neoplastic or an inflammatory lesion.
IV. Suspicious cells present, which have been seen only in the presence of a malignancy, but which might result from a bizarre inflammatory lesion.
V. Malignant cells present.

Groups I and II are regarded as negative, and groups IV and V are regarded as positive.

The results obtained by saline lavage compare favorably with the findings of other investigators. Of 53 cases of gastric cancer which were substantiated by other means, 30 or 56.6 per cent were correctly diagnosed by cytologic techniques. Five more of these cases were reported as inconclusive, so that there were only 39.6 per cent of frankly false negative reports. In addition, this series included 4 false positive reports.

The papain series shows a somewhat greater sensitivity; of 42 cases of gastric cancer proved by other means (including 2 in which the slides were unsatisfactory), 28 were reported as positive by the cytological laboratory, for a sensitivity in the whole series of 66.66 per cent. In addition, an "inconclusive" report was made in 3 instances. If the 2 cases in which the material was unsatisfactory are eliminated, only 9 false negative reports were made. The slides of these cases were reviewed, and in 2 instances diagnostic groups of cells were found which had been overlooked on the first screening. Actually, then, the technique of papain lavage could have led to false negative reports for only 7 patients or 17.5 per cent. There were 3 false positive reports in the series of 400 cases. These will be discussed in some detail later.

COMPARATIVE EVALUATION

As Figure 1 clearly illustrates, the smears obtained by the use of the papain technique are richer in cellular content than when the material is collected by saline lavage, or when undiluted material from the fasting stomach is used. This observation has been made consistently in our laboratory. The difference is more apparent when the various classifications are closely analyzed.

False negative reports. There was no consistent finding in the saline series which would account for the missed cases, except that intramural lesions were always missed. This is to be expected, perhaps, since such growths seldom exfoliate cells into the gastric cavity. The comparative rarity of such lesions prevents this characteristic from being an important problem in cytological diagnosis.

An analysis of the missed cases in the papain series revealed several interesting facts. Two of the cases, as mentioned before, were missed in screening; they occurred early in the course of the experiment and the slides were smeared too thickly. In 1 instance, the tumor was an adenoacanthoma arising in a large ulcer of the curvature. There was no apparent reason for the failure of this growth to exfoliate significant cells; lavage was adequate, as the presence of many gastric mucosal cells on the smears proved. Of the re-

maining 6 missed cases, 1 was from a case of linitis plastica in which no ulceration was observable, and 5 were cases of complete or nearly complete pyloric obstruction. It would seem apparent, therefore, that when the tumor body is accessible to the papain solution, the accuracy of the technique is quite high. At the University of California Hospital, where patients are usually seen earlier in the course of their illness than is the case at San Francisco City and County Hospital, and where, as a consequence, complete obstruction is seldom encountered, 14 of 15 proved cases of gastric cancer were reported as positive by the laboratory. In the remaining case the smear was unsatisfactory; the patient was subsequently proved to have pyloric obstruction. In the future, when subtotal obstruction is known to be present, or is indicated by the presence of food particles and detritus in the smears, a thorough preliminary washing of the stomach will be undertaken. When feasible, overnight Wangensteen suction will be done. In addition, the recently devised elimination of the contaminating precipitate has resulted in a marked increase in the ease and efficiency of screening because of the uniform concentration of cells and the absence of obscuring material.

We are convinced, as a result of this experience, that cytological technique, making use of the papain lavage, is the most promising single approach to the problem of early diagnosis of gastric cancer.

False positive reports. In both series, there were between 0.6 and 0.7 per cent false positive reports. In the missed cases of the saline series, the cells which were regarded as diagnostic were found to be, upon re-examination, vacuolated and otherwise bizarre gastric cells produced by gastritis. Such cells have been frequently encountered on routine negative papain smears. In 3 instances in the papain series, however, a large number of bizarre cells again misled the pathologist and resulted in false positive reports. These were round cells with moderate cytoplasmic vacuolization, marked variation in nuclear size, and sometimes prominent nuclear rims. They are now recognized as histiocytes, and have been subsequently found on negative papain smears.

Cytology will not achieve its full effectiveness until positive cellular findings can be regarded as diagnostic. This is not an impossible object; cytology is a young science, and cytologic appearances are in certain respects markedly different from the appearances of tissue sections. Individual cellular criteria of malignancy must be determined empirically by an examination of large numbers of patients with gastric complaints, and it is to be expected that these appearances will be deceptive so long as our experience with the technique is limited.

In our experience, papain lavage promises to decrease the percentage of false positive reports as well as increase cytologic sensitivity, since a larger number of cells are seen on the smear, and since cell relationship is better preserved. Better control of specimen handling is possible, since if normal gastric mucosal cells are not present one can assume that the specimen is unsatisfactory. Repeat washings are, therefore, desirable in such instances.

Unsatisfactory reports. In the saline series, there were 41 washings which were reported as unsatisfactory. In most instances (33 cases) the cellular material was too scanty for evaluation. In the remaining 8 instances, the specimens were unsatisfactory because of obstruction of the enteric canal. In 5 of these cases the final diagnosis was gastric cancer with pyloric obstruction.

There were only 13 cases which were reported as unsatisfactory in the papain series. In 2 instances the gastric sample was unsatisfactory because of gastric cancer with pyloric obstruction; in another the obstruction resulted from a gastric ulcer. In only 10 instances, then, were the washings too scanty to permit evaluation. In the 2 cases in which repeat washings were possible, the specimens obtained permitted diagnosis. It is probable that repeat washings will always be necessary in a small percentage of the patients examined, but papain lavage would seem to provide diagnostic material, when there is no obstruction, far more readily than saline lavage.

Number of studies necessary. That papain lavage is more efficient than saline lavage is readily born out by a comparison of the num-

ber of repeat washings necessary in the positive series. In the papain group, the diagnosis of cancer was made on the first specimen in all but 1 instance; in this case 3 washings were necessary, although inconclusive cells were reported in both of the early specimens. In the saline series, on the other hand, 3 to 5 were frequently necessary for positive diagnosis. It should be remarked that confirmatory studies on positive cases in the papain series produced equally diagnostic findings on the second attempt in every instance; in the saline series a positive report was very often followed by slides that were completely negative. It cannot be concluded that a single negative cytologic report will ever disprove the possibility of malignancy, but when papain lavages produce repeated negative findings (in the absence of evidence of obstruction) they can be considered as great assistance in ruling out a malignant lesion of the stomach.

TABLE I.—CLASSIFICATION OF PROVED CASES

	Papain		Saline	
	No. of cases	Per cent	No. of cases	Per cent
Positive	28	66.66	30	50.00
Inconclusive	3	7.14	2	3.33
Negative	9	21.43	23	38.33
Unsatisfactory	2	4.77	5	8.33
Total	42	100.00	60	100.00
False positive	3	0.72	4	0.65

EARLY DIAGNOSIS

As has been said, much of the interest in the cytological approach comes from its possibilities as an early case-finding instrument. Advanced gastric cancer is not a diagnostic problem; the need is for a technique which will be applicable in instances in which cancer is one of several plausible possibilities. The comparative ease and inexpensiveness of the technique would seem to recommend it for this diagnostic service.

Further, there is growing evidence that cytology is the most efficient means of diagnosing early lesions. In our saline series, 2 small ulcers whose x-ray appearances were questionable were proved malignant by cytologic means. At operation this diagnosis was confirmed; only local lymph nodes were invaded. In the papain series there were 3 cases in which the cytologic diagnosis was positive and x-ray findings inconclusive. Most remarkable were 2 instances in which the malignant lesions were found at operation to be preinvasive, and without lymph node metastases. In one case the x-ray diagnosis had been "benign ulcer," and in the other, "multiple polyps" with 1 questionable enlargement. In a third case, a polypoid ulcer which had been missed on the first x-ray examination was diagnosed as malignant by cytologic examination of smears; at operation it was found to be invasively malignant, but local lymph nodes were not yet involved. It is notable that the extent of the malignant lesion bore no relationship to the number of diagnostic cells seen on the smears. The 2 preinvasive lesions produced slides which were quite as diagnostic as the slides of far advanced lesions; diagnostic malignant cells were present in abundance. On the basis of the limited experience so far accumulated, it would seem that cytological methods can be expected to be quite effective in the diagnosis of early, and operable lesions, and that it is applicable to routine case-finding.

SUMMARY AND CONCLUSION

A series of 400 patients was examined cytologically, utilizing a papain solution to dissolve the mucous barrier of the gastric mucosa and thus permit the collection of a large number of exfoliated cells. This series was then compared with an earlier series of 600 cases in which the material was either a fasting gastric specimen or a saline lavage specimen.

The papain lavage series included 42 cases of gastric cancer proved by other means. Of these malignancies, 30, or 71.4 per cent, were detected by cytologic study. Two of the missed cases were due to laboratory failure to notice diagnostic cells, 2 cases had unsatisfactory slides, and in 3 instances the findings were inconclusive. Thus, there would seem to be a possible accuracy of about 85 per cent when papain lavage is utilized. In the saline series, on the other hand, there were 58 cases of gastric cancer, of which only 30 (51.1 per cent) were correctly diagnosed by the cytologic study.

It was further noted in the course of the comparison that papain lavage can contribute to an improved operability rate even beyond the improved diagnostic rate here reported. Of the 7 false negative reports in this series, 5 obviously resulted from subtotal or complete pyloric obstruction. At the same time, cytologic studies utilizing papain lavage permitted the diagnosis of 2 cases in which the cancer was noninvasive, and 1 in which some invasion was noted but in which there was no invasion of local lymph nodes. Further, in all but 1 instance, the use of the papain technique permitted positive diagnosis with only 1 specimen, and repeat examinations consistently confirmed the original positive finding.

The problem of false positive reports remains, but further experience with the cytologic technique can be expected to minimize this hazard. Papain lavage, by increasing the amount of cellular material in the cytologic specimen, should contribute to the resolution of this problem. It is the authors' conviction that the use of papain can go far toward making cytology the diagnostic technique that is required for an effective approach to the problem of gastric cancer.

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FIBRINOLYSIS IN SURGERY PATIENTS

I. Possible Relationship to a Hemorrhagic Diathesis

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THE aseptic breakdown of whole blood clots in vitro has been known for over a century, but it has only been in the past few years that the possible significance of increased plasma proteolytic activity in vivo has been recognized. Although normal whole blood clots will remain intact in a test tube for days or even weeks, blood drawn under certain circumstances will coagulate but the clot will, in a matter of minutes or hours, disintegrate and disappear. In 1893 Dastre described this phenomenon in blood from dogs who had been bled extensively and gave it the name "fibrinolysis."[1]

In the past 15 years a number of investigators have studied the process of fibrinolysis and have demonstrated that an increase in plasma proteolytic activity is due to the activation of a precursor normally present in plasma to an active enzyme, fibrinolysin (plasmin). This enzyme has been shown to cause the dissolution of fibrin and fibrinogen, and, if present in sufficiently high concentration, the breakdown of accelerator globulin and prothrombin as well.

MacFarlane has reported the occurrence of fibrinolysis in diluted human plasma under a variety of circumstances and has suggested that changes in the amount of this enzyme might alter the normal coagulation mechanism (1, 5, 6). In 1946 Tagnon and associates (9) reported that 5 of 13 dogs exhibited this phenomenon after the induction of hemorrhagic shock; a significant reduction in plasma fibrinogen levels was shown to accompany the fibrinolytic process. Proteolysis was also demonstrated in the blood of 7 patients in shock and 1 with severe anoxia.

In 1949 Moloney and co-workers reported a case of abruptio placenta with total afibrinogenemia and a severe hemorrhagic diathesis which was corrected successfully with intravenous fibrinogen. Weiner and associates subsequently described a similar case with marked fibrinolysis; the associated hemorrhagic state responded almost immediately to parenteral fibrinogen.

Surgeons are occasionally confronted with a hemorrhagic diathesis characterized by capillary bleeding from virtually every site of trauma; each vessel along the wound surface and in the operative field appears to ooze blood. In spite of heroic efforts the patient frequently dies in hemorrhagic shock, although occasionally massive transfusions have carried the patient through this complication. A recent report describes 7 patients with a bleeding tendency of this type, but no studies for plasma proteolytic activity were carried out (3).

It was felt that this infrequent but often fatal hemorrhagic diathesis might feasibly be produced by activation of a proteolytic enzyme system with subsequent lysis of hemostatic fibrin clots, as well as the fibrinogen from which these clots are formed, resulting in the induction of uncontrollable bleeding.

Four patients were studied while in profound shock during cardiac arrest and following resuscitation. Each exhibited plasma fibrinolytic activity of varying degrees of severity. Two demonstrated the classical picture of a hemorrhagic diathesis; the bleeding tendency in both cases was controlled satisfactorily with intravenous fibrinogen after multiple transfusions had proved of no benefit.

A patient with extensive carcinoma of the stomach was also found to have an abnormal but not an extremely severe bleeding tendency

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[1] "Fibrinolysis," "lysis," and "proteolysis" are considered as synonymous terms in this report. The latter term is used interchangeably since the fibrinolytic enzyme has subsequently been demonstrated to cause breakdown of plasma fractions other than fibrin.

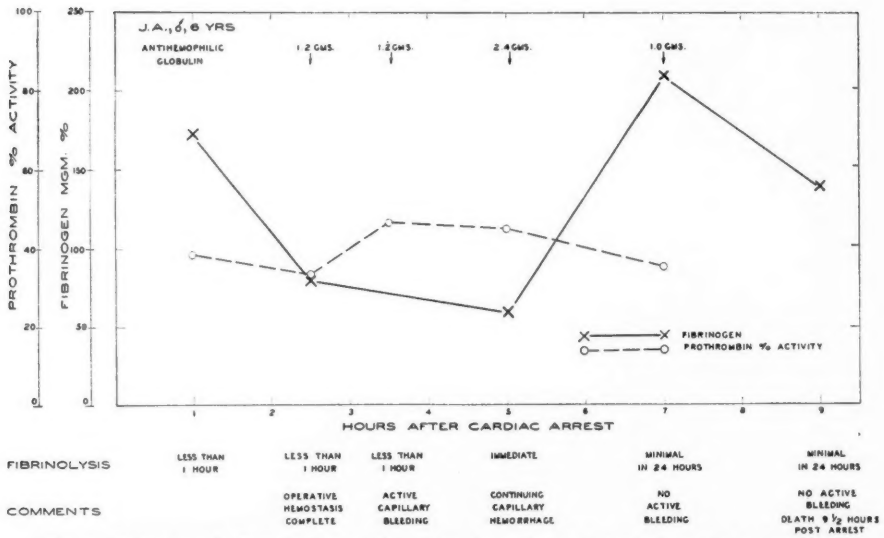

Fig. 1. Laboratory findings in Case 1, illustrating the action of fibrinolysin on fibrin clots and on fibrinogen as well. Bleeding ceased and plasma fibrinogen rose following the injection of 2.4 grams of antihemophilic globulin.

associated with increased plasma proteolytic activity and decreased plasma fibrinogen levels; similar laboratory findings were demonstrated in a patient with bronchogenic carcinoma.

METHODS

Prothrombin determinations were performed, using the one stage Quick procedure. Fibrinolysis was recorded as the time required for complete lysis of the patient's whole blood clot at 28 degrees C. Plasma fibrinogen was determined as clottable protein by the Biuret method (12). Normal values ranged from 150 to 400 milligrams per cent, most values being between 250 and 300 milligrams per cent.

The source of fibrinogen used intravenously was antihemophilic globulin as supplied by Dr. Harlan Anderson of the Michigan Department of Health. Various lots of this product, assayed for fibrinogen, were found to contain 35 to 50 per cent clottable protein.

RESULTS

The pertinent data and laboratory findings of 4 of the patients mentioned above follow:

CASE 1. A white male, aged 6 years, was noted on a school examination to have a swelling of the left mandible. X-ray films of the mandibular tumor demonstrated a moth-eaten appearance. A biopsy elsewhere had been unsatisfactory because extensive hemorrhage prevented removal of an adequate specimen. However, there was no other evidence to suggest a bleeding tendency. Physical examination on admission was negative except for the presence of a 2 by 2 centimeter hard tumor on the left mandible 2 centimeters from the midline.

Because of the chance of malignancy, rebiopsy was attempted under gas-oxygen-ether anesthesia. Immediately after removal of the biopsy specimen, severe bleeding occurred from the biopsy wound. Blood was being administered under positive pressure when sudden cessation of heart beat was noted. Thoracotomy was performed and cardiac massage instituted within 1½ minutes from the time of recognition of cardiac arrest. Approximately 25 minutes later normal heart action had resumed; complete hemostasis in the thorax was obtained, and, after a few minutes of observation, the chest was closed. Blood coagulation studies during the patient's subsequent course are shown in Figure 1. Complete lysis of the patient's whole blood clots in vitro occurred within 1 hour on repeated occasions over a period of 5 hours following the onset of cardiac arrest. Because extensive hemorrhage was noted via the thoracostomy tube, 2 hours following the initial closure, the chest was reopened and multiple small bleeding areas over the heart and chest wall controlled; at the time of reclosure of the chest wound, no bleeding was apparent. One hour later, the approximate time required for fibrinolytic breakdown

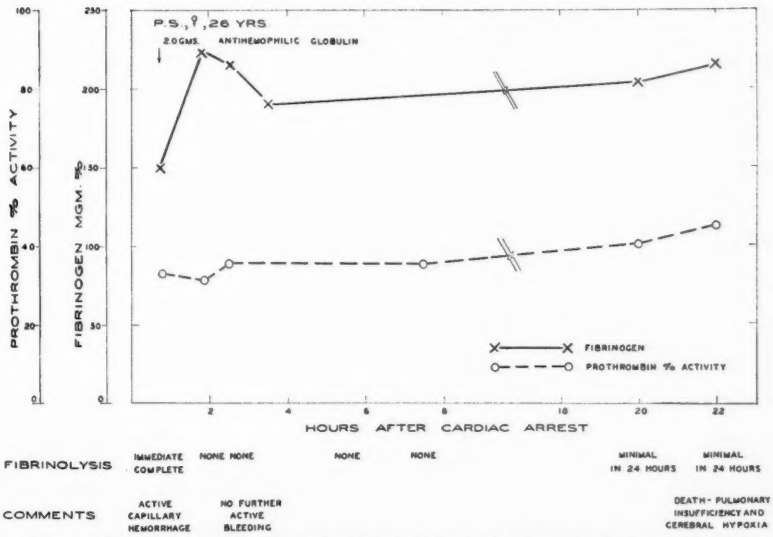

Fig. 2. Case 2. A hemorrhagic diathesis probably resulting from the action of fibrinolysin on fibrin per se. Fibrinogen levels are adequate. Immediate cessation of bleeding following the injection of 2.0 grams of antihemophilic globulin.

of hemostatic fibrin clots, evidence of recurrent hemorrhage was noted; 9,000 cubic centimeters of blood administered during the bleeding episode did not appear to influence the hemorrhagic process.

One and two-tenths grams of the antihemophilic globulin was administered at the 2 occasions noted, but because this dosage appeared inadequate to control the hemorrhage, 2.4 grams was administered 5 hours post arrest at a time when severe hemorrhage was occurring. Soon thereafter the patient's bleeding stopped, and no recurrence of hemorrhage was noted prior to the patient's demise. During the 2½ hours prior to the last and effective dose of antihemophilic globulin the patient's plasma fibrinogen levels, as later determined, were too low to provide sufficient fibrin for adequate hemostasis. Following administration of this preparation containing fibrinogen, however, the plasma fibrinogen rose and remained at adequate levels until the time of death.

Unfortunately 9½ hours following the initial cardiac arrest, a second cessation of heart action occurred and further cardiac massage was unsuccessful. Death was attributed to cerebral hypoxia.

CASE 2. A 26 year old white female was admitted for operative treatment of advanced pulmonary tuberculosis. She had a 6 year history of tuberculosis and on physical examination showed signs of a chronic illness. There was no history of any prior hemorrhagic tendency. Admission prothrombin activity was 100 per cent.

Soon after admission a right first stage thoracoplasty was performed without incident; the postoperative course was uneventful.

Three weeks later a right thoracotomy was carried out for removal of tuberculous bronchiectatic right upper and middle lobes. During the hilar dissection the patient's blood pressure fell to 80/60; the operation was discontinued and the patient's blood pressure was restored and maintained by the intravenous administration of norepinephrine. After a period of 45 minutes the blood pressure had again stabilized at 120/80. The operative procedure was then completed without difficulty. An estimated blood loss of 7,000 cubic centimeters was completely replaced with whole blood. During the closure of the chest, however, it was noted that the patient was losing excessive amounts of blood from multiple small bleeding points in the extracostal muscles. Soon thereafter the anesthetist reported an absence of blood pressure and pulse. The chest was immediately reopened; cardiac standstill was observed, and effective cardiac massage was instituted within 3 to 5 minutes after the recognition of cardiac arrest. After 27 minutes of massage, the heart resumed normal rhythm, and a blood pressure was obtained at 80/60. Hemostasis was obtained, and the chest was again closed. Soon thereafter, however, continued excessive hemorrhage was noted from the thoracostomy tube. An additional 2,140 cubic centimeters of whole blood had no effect in alleviating the bleeding process. One and one-half hours after the onset of cardiac arrest and less than ½ hour after the redevelopment of the hemorrhagic state, 2.0 grams of antihemophilic globulin was administered intravenously in 100 cubic centimeters of physiologic saline. Within ½ hour bleeding had stopped and did

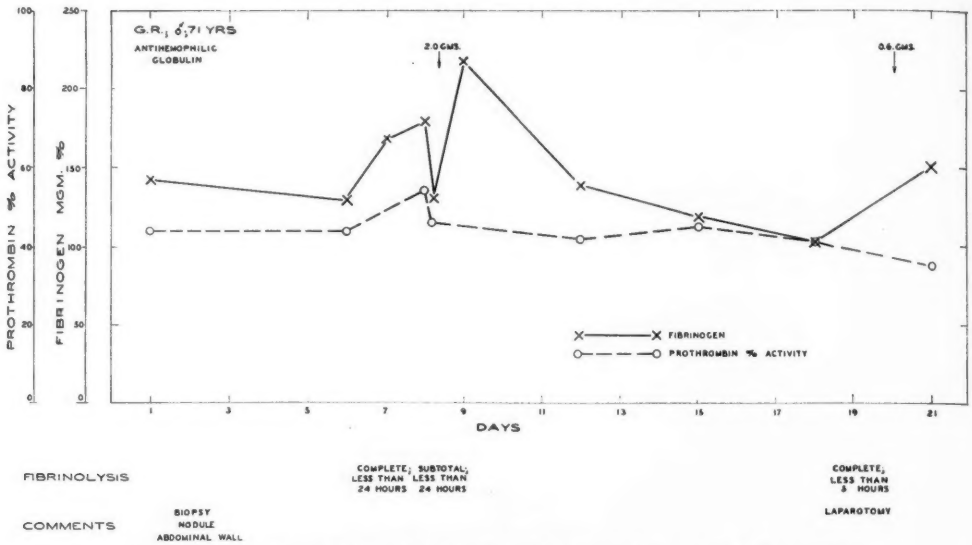

Fig. 3. Case 3. Repeated fibrinolysis in a patient with extensive cancer of the stomach.

not recur prior to death 21 hours later. Laboratory studies during the patient's course are shown in Figure 2. The first blood specimen obtained clotted and then lysed completely within several minutes.

The patient was maintained in the operating room on assisted respirations with a helium-oxygen mixture. She steadily continued to improve for the first 16 hours following the cardiac arrest and was able to move her arms and legs, respond to direct commands, and speak to the attending physician. Subsequently, however, the blood pressure began to fall from its previous level of 100/80; respiration became more labored and the patient expired 22½ hours following the onset of cardiac standstill.

At autopsy the right chest was found to be filled with clotted blood, and the remaining right lower lobe was completely atelectatic. The cause of death was thought to be related to insufficient pulmonary reserve, cerebral hypoxia, and debilitation from a chronic illness.

A third patient in hemorrhagic shock had a less marked degree of fibrinolytic activity; hemorrhage was not a prominent feature in this patient's course.

In another patient who developed cardiac arrest following the completion of a thoracoplasty, complete lysis of whole blood clots occurred repeatedly in 1 hour. When 100 milligrams of an exogenous source of 95 per cent fibrinogen were added to the tube containing this patient's blood which had previously lysed, a clot again formed, but complete dissolution of this second clot also occurred within 30 minutes. This patient, however, lived for only a short period following cardiac resuscitation, and during this interval no extensive hemorrhage was noted.

Fibrinolysis was also demonstrated repeatedly in a patient with extensive cancer. This proteolytic process was sufficiently severe to lower the patient's plasma fibrinogen to subnormal levels and was thought to contribute to the prolonged bleeding that occurred intermittently for 1 week following a biopsy wound and for unusual capillary bleeding encountered at a subsequent laparotomy. The case history follows.

Case 3. A 71 year old white male was admitted with a 2 month history of epigastric distress, vomiting, and a 42 pound weight loss. There was a large palpable left upper quadrant mass. Gastrointestinal x-ray films demonstrated neoplastic replacement of almost the entire stomach.

Five days following admission a suspicious subcutaneous nodule to the left of the umbilicus was biopsied and subsequently was found to be nonmalignant on microscopic examination. Several hours following the biopsy, continued bleeding into the wound necessitated secondary hemostasis after the evacuation of a large hematoma. Unfortunately, no studies of plasma proteolytic activity were obtained

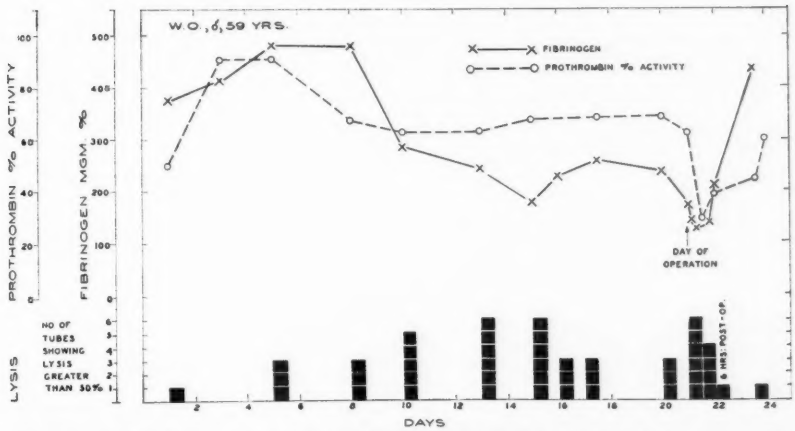

Fig. 4. Fibrinolysis in a patient with bronchogenic carcinoma. As the fibrinolysin titer increased there was a simultaneous, inversely proportional, decrease in plasma fibrinogen. A rapid decrease in fibrinolysin occurred after removal of the neoplasm; plasma fibrinogen rose to 4 times the operative level.

at that time. During the next week the patient continued to bleed intermittently from the biopsy wound; on the seventh day following the biopsy, because of continued bleeding, operative evacuation of a large hematoma was carried out and the wound was packed in order to secure hemostasis. No major bleeding points were seen. It is interesting that on the day prior to this procedure clotted blood, obtained for other studies, completely lysed on standing overnight. A blood sample drawn just prior to the packing showed subtotal lysis in 24 hours. Because of the above-mentioned hemorrhagic tendency this patient was given intravenously 2.0 grams of antihemophilic globulin at the time of operation. Although the bleeding stopped shortly thereafter, it was impossible to evaluate whether the packing of the wound or the administration of fibrinogen had been responsible for cessation of this process. It is interesting to note that the patient's plasma fibrinogen was significantly elevated on the following morning (Fig. 3).

Laparotomy was performed 13 days later but extensive invasion and metastatic involvement by the neoplasm made a palliative resection impossible; a jejunostomy was performed. During the procedure the patient bled excessively from the wound surface; 0.6 gram of antihemophilic globulin was administered as the wound was closed; no postoperative bleeding was noted.

Postoperatively, the patient became progressively weaker and unresponsive and succumbed on the third day following the latter procedure. Autopsy confirmed the extensive nature of the neoplasm.

Unfortunately adequate facilities for study of plasma proteolytic activity were not available until the last few days of this patient's life, and, so, studies of fibrinolysis were very sporadic. This case is presented merely to demonstrate that fibrinolysis can occur repeatedly in a patient who is neither in shock nor anoxic, and that such a persistent proteolytic phenomenon might have been responsible for the unusually low fibrinogen levels and abnormal bleeding tendency observed in this patient (Fig. 3).

Subsequently, a patient with an operable bronchogenic carcinoma was studied extensively during his preoperative and postoperative course for changes in fibrinolytic activity by the MacFarlane plasma dilution method which is thought to be a more sensitive indicator of less marked increases in plasma proteolysis. As the fibrinolytic activity increased there was a significant fall in plasma fibrinogen levels which showed a definite inverse relationship to changes in plasma fibrinolysin content. Figure 4 shows the changes that took place; the marked fall in proteolytic activity and rise in fibrinogen following removal of the neoplasm is striking.

The MacFarlane procedure, as modified by the authors, involves the observation for clot lysis of 6 plasma-saline dilutions, from 1:2 through 1:64, at 28 degrees C. for 24 hours; thrombin topical is used to produce clotting

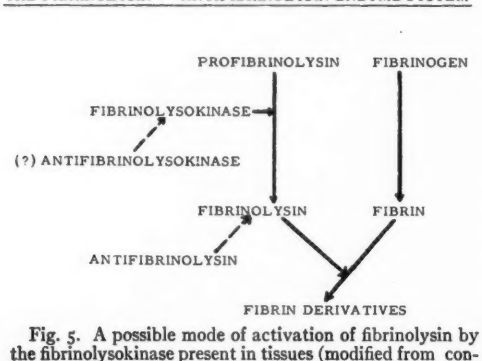

Fig. 5. A possible mode of activation of fibrinolysin by the fibrinolysokinase present in tissues (modified from concepts of Lewis and Ferguson). The active enzyme will break down fibrinogen as well as fibrin.

of the oxalated plasma. Usually the highest dilutions are the first to show proteolytic activity, but occasionally tubes with lesser dilutions will show greater proteolysis. The authors believe that proteolytic activity might well be accentuated in higher dilution because the inhibitor, antifibrinolysin, is then diluted out; Tocantins has demonstrated a phenomenon of a similar nature in his experiments with lipid antithromboplastin. In Figure 4, proteolytic activity has been recorded as the number of tubes (set up according to the above-mentioned dilution technique) in which a gross estimation of greater than 50 per cent lysis of the fibrin clots had occurred. This is admittedly a very gross qualitative estimation of changes in lytic activity. It has been shown, however, that a number of normal individuals have consistently negative estimations of proteolytic activity by this method.

DISCUSSION

The cases of cardiac arrest are presented, in spite of the patients' ultimate demise, because prolonged existence of hypotension tends to accentuate the magnitude of the increase in plasma proteolytic activity and the severe nature of the hemorrhagic state. The first 2 cases demonstrate the more extreme forms of hemorrhagic diathesis and are illustrative of the changes in plasma proteolytic activity that appear to accompany this condition. The relationship of extensive bleeding to the increased fibrinolytic activity and decreased fibrinogen levels in these cases is such that one might postulate that this proteolytic phenomenon could be responsible for the onset and persistence of uncontrollable hemorrhage.

A possible mechanism for interruption of the homeostatic balance between fibrinolysin (plasmin) and its antagonist may be proposed from existing knowledge of this enzyme system (Fig. 5). The antagonist of fibrinolysin, antifibrinolysin, and the inactive precursor, profibrinolysin (plasminogen), are normally present in plasma. The fibrinolysokinase which activates profibrinolysin to fibrinolysin has been shown to be present in serum, certain bacteria, and in the microsome fraction of most animal tissues.

It might be theorized that this lytic process would be activated by any pathological state producing increased tissue necrosis, whether it be shock, anoxia per se, or cancer. Tissue breakdown could cause release of the enzyme activator present in the cell microsome fraction; this fibrinolysokinase could then convert the precursor to active fibrinolysin. With increasing activation of this enzyme, antifibrinolysin could not antagonize all the fibrinolysin present, and fibrin and fibrinogen breakdown would result. Such proteolytic breakdown of fibrinogen and of the hemostatic fibrin clots formed at the time of operation would appear to be a feasible explanation for the mechanism of induction of a hemorrhagic state.

As mentioned previously, Tagnon and coworkers (9) produced a very similar picture in 5 dogs following the induction of hemorrhagic shock. They were able to demonstrate marked fibrinolysis and an associated fall in plasma fibrinogen. It is interesting to note that in 5 of the 8 remaining animals who did not show whole clot lysis there was a decrease in plasma fibrinogen content of 50 to 70 per cent. The findings in the patient illustrated in Figure 4 suggest that the plasma dilution technique might have demonstrated a fibrinolytic process of lesser severity in these dogs also; the method of whole clot lysis requires very marked increases in proteolysis before a positive result is obtained. It is our feeling that a progressive decrease in plasma fibrinogen, concurrent with evidence of increased

proteolysis by the plasma dilution method, is indicative of a lesser degree of lysis, as demonstrated in this patient.

The prolonged presence of increased plasma proteolytic activity in association with malignant disease is demonstrated by Case 3 and by the patient illustrated in Figure 4. The fibrinolytic activity in these patients was of a lesser degree of severity. Persistently low fibrinogen levels, found when this process was active, suggest that fibrinogen was being lysed continually in vivo. Hypotension during surgery in these patients could have increased the proteolytic breakdown of more fibrinogen and thus made bleeding more pronounced and a true hemorrhagic diathesis more likely, since proteolysis of a lesser degree and a shorter duration would have been necessary to lower an already borderline plasma fibrinogen to a level inadequate for the formation of hemostatic fibrin clots. It is impossible to say whether the small amounts of fibrinogen administered in Case 3, at the time of packing of the biopsy wound and subsequently at laparotomy, prevented a more extensive hemorrhagic process.

Cancer itself appears to be related in some way to the activation of the fibrinolytic process, since removal of the bronchogenic carcinoma in the latter case (Fig. 4) resulted in almost immediate disappearance of fibrinolysis and rapid increase in fibrinogen to 4 times the lowest preoperative level. Similar patterns have been found subsequently in patients with varied types of neoplasms. A recent report describes 2 patients with extensive metastatic carcinoma of the prostate who demonstrated increased fibrinolysis and who subsequently developed a severe hemorrhagic diathesis (10). However, no plasma fibrinogen levels were determined in either case.

Thus it appears possible that one or a combination of two factors may be responsible for this type of bleeding tendency. Irrespective of a normal or at least adequate plasma fibrinogen level, fibrinolysin is capable of breaking down fibrin clots formed at the site of vascular trauma, resulting in recurrent hemorrhage (as in Case 2). On the other hand, proteolytic destruction of fibrinogen per se can lower plasma fibrinogen to such a low level that adequate hemostatic fibrin clots cannot be formed at the site of operative or accidental damage to a blood vessel; this latter pattern alone is probably more common following prolonged moderate increases in proteolytic activity, similar to the changes seen in neoplastic disease. Sudden marked increases in fibrinolytic enzyme, if persistent over a period of hours, appear to act first on fibrin, but they also lower substantially the blood fibrinogen content (as illustrated in Fig. 1).

Moderate depression of prothrombin activity to 30 to 65 per cent of normal activity was noted in all of the patients studied. Except for the case illustrated in Figure 4, this decrease is probably not related to the proteolytic process, although fibrinolytic destruction of accelerator globulin could produce a change of this magnitude which could not be differentiated by the Quick method from a fall in true prothrombin values. In the case reported by Weiner and co-workers, a more significant decrease in prothrombin was found.

In the first 2 cases at least, the rapid cessation of bleeding after the administration of adequate amounts of fibrinogen intravenously is very suggestive that this plasma fraction may prove of definite therapeutic value. The first case illustrates the need for administration of large doses of this agent in order to obtain a satisfactory effect; injection of several small doses of fibrinogen appeared to be of little or no value; the cumulative effect of over 2 grams of injected fibrinogen was apparently necessary to halt the bleeding process.

The amount of fibrinogen required to correct this abnormality must certainly be related to the amount of proteolytic activity and to the extent of fall in the patient's own plasma fibrinogen. Both of the patients presented had very small blood volumes because of their small size and weight and, therefore, had a lesser total circulating fibrinogen than one might see in an adult male. In a normal individual, then, with a total plasma fibrinogen of 8 to 15 grams it seems reasonable to assume that at least 3 or more grams of exogenous fibrinogen might well be necessary to correct a hemorrhagic state of similar severity. Moloney and associates injected 4.8 grams of fraction I, whereas Weiner and co-workers

used 2.4 grams of fibrinogen; the purity of these preparations, however, was not stated.

The ultimate survival of the patient, following this type of hemorrhagic state, depends also on correction of the underlying pathological process which may have contributed to the production of such a bleeding tendency. If, as we propose, shock or anoxia or cancer is responsible for the activation of the proteolytic enzyme causing this bleeding, these etiological factors must be eliminated before the patient can recover. The administration of fibrinogen is designed to correct temporarily the existing plasma fibrinogen deficit, and to aid in the formation of essential hemostatic clots, while the factors contributing to the activation of the fibrinolytic mechanism are being alleviated, if possible. Although both patients with cardiac arrest had rapid cessation of their bleeding following fibrinogen therapy, the short period of cerebral hypoxia in one case and insufficient pulmonary reserve in the other were of such severity as to prevent the satisfactory recovery of these patients.

SUMMARY

Markedly increased plasma proteolytic activity has been found in 4 patients with profound shock. Two of these patients demonstrated a severe hemorrhagic diathesis. The administration of human fibrinogen intravenously appeared to be a rational and apparently successful method of therapy for this bleeding state.

Two patients with cancer were found to have increased fibrinolysis of a lesser magnitude. Simultaneous with the occurrence of fibrinolysis was a decrease in plasma fibrinogen to levels borderline or inadequate for the formation of hemostatic fibrin clots. One patient demonstrated an abnormal bleeding tendency.

A possible explanation for the mechanism of production of this hemorrhagic diathesis in surgery patients is proposed.

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A REAPPRAISAL OF ABSORBABLE GLOVE POWDER

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SEVERAL years ago, in association with Doctor E. P. Lehman, one of the present authors presented a report (3) dealing with the dangers of talcum powder as a glove lubricant, and describing studies of a powder derived from corn starch as a suitable replacement for talcum. These findings were subsequently confirmed by other investigators, and a recent sample survey indicates that talcum has been replaced by the starch derivative powder in the operating rooms of 60 to 90 per cent of the hospitals in the United States.

It has been well established that this starch derivative powder is vastly superior to and less hazardous than talcum powder. However, as is so often the case when a new therapeutic agent is developed, there is a tendency to lose sight of its limitations. When one hazard has been eliminated, whether partially or completely, it is easy to fall into the trap of assuming that the illusory "foolproof preparation" has been achieved and to throw caution to the winds. A widespread impression seems to have developed that starch powder is "perfectly safe." There has been a tendency to discard entirely the scrupulous effort to minimize powder contamination of the operative field, which was encouraged when talcum powder was in general use. A growing appreciation of this dangerous trend, together with a recognition of certain deficiencies in the earlier studies, has prompted experimental reappraisal of the effects of absorbable glove powder.

Evaluation of the effects of glove powder is based on several basic considerations from both the clinical and experimental standpoint.

1. The production by contaminating powder of adhesions on serosal surfaces or of granulomas in the soft tissues is the result of a foreign body reaction.

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2. The production of adhesions and granulomas by contaminating talcum powder is the result of both chemical irritation and a foreign body reaction, although the latter clearly predominates. The fact that talc crystals are insoluble, and for practical purposes nonabsorbable, makes the reaction essentially an irreversible and permanent one.

3. Within limits, treated starch powder has been shown to produce a much less violent reaction than does talc. Provided all other factors conducive to inflammatory reaction and adhesion or granuloma formation are excluded, starch powder appears to be completely absorbed and it leaves the serosal surfaces and soft tissues undamaged. But until absorption takes place, the starch granules constitute as much of a foreign body as would any other powder of comparable particulate size. The longer the granules remain unabsorbed, the more advanced the foreign body reaction will be, and the less chance there is that it will be reversible. When a complicating factor such as infection is added to the foreign body reaction of tissues, the process is much more violent and the extent of permanent scar tissue formation is proportionately increased. These facts have apparently been overlooked, and the oversight has led to an exaggerated confidence in the safety of treated starch as a glove powder.

In our previous animal experiments, which demonstrated the superiority of treated starch over talcum powder, the interval between implantation of the test material and re-examination of the contaminated peritoneum was 3 weeks. It was shown that under ideal conditions, starch powder was absorbed without ill effect, as compared with dense adhesion and granuloma formation when talc was used, but no studies were included to evaluate the reaction to starch during the 3 week interval. It is apparent that any absorbable foreign material, including the famil-

iar surgical catgut, produces a tissue reaction before it is absorbed and that the severity and final effect of this reaction depends on a variety of factors.

It is not within the scope of the present discussion to review in detail the pathological physiology of the foreign body reaction. In spite of the extensive literature, really fundamental study of this subject is still in its infancy and conclusive information is very meager. E. P. Lehman, coauthor of our previous publications on treated starch, has recently summarized (4) the information that is available regarding the reaction of living tissues to foreign materials. His thought-provoking appraisal of this complex problem should serve the double purpose of stimulating further study and of reaffirming the dangers inherent in the use of even the best absorbable materials in surgery. One paragraph of Lehman's discussion is particularly pertinent to the considerations to be presented here:

"It is clear that any discussion of the tolerance of tissue for foreign material must be based on the assumption that infection is absent. Gross infection is easy to recognize, but minor degrees of contamination by bacteria, promptly controlled without resulting gross infection, are not easy to measure in experimental studies. And yet, the minimal inflammatory reaction accompanying the destruction of undetermined bacterial contamination may modify the extent and the quality of the tissue reaction to the foreign material itself. *It must be recognized in all studies of the foreign body reaction that this indeterminate factor may be present.* With this reservation always in mind, let us try to define what is meant by tissue tolerance."

He goes on to list and to comment upon the multiple variables which influence the reaction of tissues to foreign material. These include: (1) the size and nature of the wound; (2) the amount or particulate size of the foreign material; (3) the wetability of the material; (4) the physical quality and behavior of the material, including electric potential, crystalline structure, piezoelectric qualities, and radioactivity; (5) chemical characteristics of both the material and the host, including soluble and insoluble impurities, formation of secondary substances by the interaction of the material with the serum or interstitial fluid of the host, cytotoxic effects, hydrogen ion concentration, tissue enzymes, and protein reactions; (6) variations in the host, such as specific responses of a given type of tissue, or differences in the host as a complete organism (Thus the response may vary in the same individual under different conditions of health and disease, or individual and species differences may be pronounced.); (7) antigen-antibody reactions.

Even this brief recapitulation of the factors to be considered in estimating the effect of a glove powder in tissue should be sufficient to indicate the caution with which any such powder should be used. Little fundamental information is available about the reaction of tissues to starch, either treated or untreated.

In this connection, and at the risk of free quotation to the point of plagiarism, another of Lehman's comments is important. He says: "The traditional empirical method of testing materials for surgical use in the tissues of animals and man is not profitable from the fundamental point of view. It remains necessary, however, in this era of heretofore unknown chemical compounds. Until prediction is possible, every new compound with possible surgical usefulness must be tested empirically, [though] it is a wasteful and uncertain method."

In common with our own and other previously reported studies, the work here presented is of an empirical nature and subject to the limitations inherent to that approach. Moreover, it does not provide answers to a number of questions which might be sought on an empirical basis. It is believed, however, that convincing evidence is afforded in support of the conclusions which follow, the application of which to surgical practice seems important.

OBJECTIVES OF THE PRESENT STUDY

The starch powder now in general use consists (1) of "a biologically absorbable powder prepared from corn starch by etherification with epichlorohydrin. The starch polymer chains are presumably cross-linked by 1, 3 diether glycerin groups to the extent of not more than 2 per cent of the original starch weight. The starch derivative powder is mixed with 2 per cent magnesium oxide, and contains small residual amounts of sodium sulfate and sodium chloride."

Various investigators, including ourselves, have demonstrated the complete absorbability of this preparation in living tissue. The "tanning" process with epichlorohydrin renders the starch granules resistant to autoclaving but cannot be shown to affect either the tissue tolerance or the absorbability of the starch, as long as it is well dispersed in fine particles. It is obvious that "clumps" or masses of this or of any other powder imbedded in tissue will produce more reaction and absorb more slowly. It is desirable, therefore, from the standpoint of both lubricating qualities and tissue tolerance, to keep the powder as finely dispersed as possible. In the original development of the experimental powder (2), 10 or 12 different dispersal agents were tested. For various reasons, only magnesium oxide and magnesium carbonate were found to be acceptable. In the commercial preparation, as noted above, magnesium oxide in 2 per cent concentration is added as a dispersal agent. Although our previous studies indicated that this addition, in the concentration used, was harmless to tissues, some question was raised about it. Seelig believed, on the basis of tests for aldehyde with Schiff's reagent, that paraldehyde had been used in the tanning process. Postlethwait and his associates (7) demonstrated that the faintly positive reaction with Schiff's reagent was due to the presence of magnesium hydroxide, derived in solution from the magnesium oxide dispersal agent. Further chemical studies by Davis and George showed that after prolonged storage, appreciable amounts of the magnesium oxide are converted to magnesium carbonate. It seems possible, therefore, that a more stable glove powder might result from the initial use of magnesium carbonate as the dispersal agent. This was one of the two agents found to be acceptable in the original studies, although to be effective, a 3 per cent concentration must be used, as compared with 2 per cent of magnesium oxide.

One purpose, then, of the present study has been to compare, under standard conditions, the relative tissue tolerance toward two identical starch powders in which magnesium oxide and magnesium carbonate, respectively, have been added as dispersal agents.

Another question to which an answer has been sought is the degree and extent of peritoneal reaction which takes place during the interval of 6 to 25 days prior to complete absorption of the powder. This question has already been studied to a limited extent in both dogs and rabbits by Postlethwait and his associates. They found that the rate of absorption of the powder varied considerably, from as little as 24 hours to as much as 12 days. Their study illustrates the very marked species and individual variation in tissue reaction to foreign bodies and in adhesion formation. The great difference among individuals, in their tendency to form adhesions and in their ability to absorb them, is familiar to all clinical surgeons, and it is one of the variables mentioned by Lehman as contributing so much to the inaccuracy of empirical experimental studies. It was felt that if tests were made on a larger series of animals, statistically significant comparisons might be achieved.

It was believed that the study might produce evidence to emphasize the fact that in spite of the demonstrated superiority of treated starch over talcum powder as a glove lubricant, due precautions should nevertheless be taken to minimize contamination of any wound with starch powder, since no foreign material, even if it is ultimately absorbable, is entirely innocuous.

METHOD

The basic procedure of the present study is essentially the same as that previously employed. Dogs were used in all the experiments because it is believed that the reaction of the canine peritoneum more nearly approximates that in the human patient than is the case with other experimental animals. The dog is large enough to permit a closer experimental parallel with conditions in a standard operation on a human patient. The experimental cycle consisted of laparotomy under careful aseptic conditions with delivery of the small bowel. In test animals, the entire small bowel and mesentery from the ligament of Treitz to the ileocecal valve was dusted as evenly as possible with a measured amount of test powder. No matter how carefully this was done, the distribution was uneven, with clumps of

powder, obviously difficult to absorb, in some areas, and with finely dispersed particles in others. This fact is important and will be commented upon later. In control animals, the bowel was handled in an identical way but no powder was applied. In all operations, gloves were first carefully washed in running water.

After intervals ranging from 1 day to 25 days, the animals were either sacrificed or reoperated upon through a new incision on the opposite side of the abdomen, and the adhesions were counted, using the method of Lehman and Boys (5). As these authors have pointed out, this represents only "an exceedingly rough quantitative estimation of results," but to our knowledge it is the only method available for a quantitative comparison of the effects of various agents. To express these results in numerical terms is inaccurate to a degree, and exposes them to considerable misinterpretation. Bearing in mind the many variables emphasized by Lehman, the presence of 8 or 10 fine, tenuous adhesions in an otherwise clean and glistening peritoneum may actually indicate much less reaction than 4 or 5 large sheet-like adhesions between mesentery and mesentery, bowel and bowel, or mesentery and bowel. Hence, *too much emphasis should not be placed on the numerical results*. We have, therefore, attempted to compensate for this obvious inaccuracy by illustrating the differences photographically. Nevertheless, the numerical count of adhesions in a large enough series of animals has some comparative statistical significance.

As a further check on the gross observations, representative adhesions were removed en bloc when present, and paraffin sections were prepared for microscopic examination under normal and polarized light. In the same animals, the lymph nodes at the root of the mesentery were also removed for similar study. It was hoped that the character and degree of inflammatory reaction might throw some light on the presence or absence of subclinical infection. Since intact starch granules are readily identified under polarized light (by the characteristic maltese cross), it was also hoped that the progress and mechanics of absorption might be followed. These efforts met with only very limited success.

PROCEDURE

In all of the present experiments on dogs, the test dose of powder was ½ teaspoonful. For reasons indicated in our previous report, a volumetric measure appeared to be preferable to a weighed dose, and in the earlier studies ½ teaspoonful of starch derivative powder was found to weigh approximately 1.0 gram. This is a large dose in the peritoneum of a dog and constitutes a much more severe test of the powder than would ever be likely to occur in clinical practice, even after perforation of a glove. It represents the rough equivalent of *all* the powder that can be washed from the surfaces of 8 pairs of surgical gloves which have been prepared for routine use in the operating room.

In the course of this study, 100 dogs were operated upon. This large number of dogs taxed our kennel facilities severely and it was impossible to keep each animal long enough, before operation, to be sure that he was in good physical condition. Many dogs were operated upon the same day or the day after they were received from the dealer. As a result of this, 16 dogs died of distemper or of its complications, before the assigned day for their second operation and adhesion count. In 3 other dogs, the test was invalidated by obvious wound infection. In 1 dog, the proper identification of the test powder was questionable and this animal was, therefore, eliminated from the series. Thus 20 out of 100 animals were invalidated.

The remaining 80 dogs, whose wounds healed without gross evidence of infection and who were re-examined on schedule, still left much to be desired in terms of general physical condition. Virtually all of them were infested with worms, malnutrition was common, and many had been previously used in another series of experiments dealing with the healing of small burns of varying depths on the skin of the back. Thus a wide range of variables was introduced, which may explain why a few adhesions were produced even in the control dogs where no powder was applied to the peritoneal surfaces. It must be remembered, however, in terms of the application of the experimental results to clinical surgery, that ideal conditions are seldom achieved when the

human peritoneum is exposed. In appendicitis, perforated ulcer, or intestinal resections of any kind, either bacterial or chemical contamination, or both, are present in varying degree. Where hemoperitoneum, either prior to or as a result of surgery is encountered, another variable is introduced. The relationship of the enzymes associated with malignancy to foreign body reaction is entirely unknown, so that in operations for human abdominal carcinoma, still another variable is present. Therefore, since the study was designed to simulate actual conditions in human clinical surgery, the fact that the dogs were not uniformly in perfect health did not seem necessarily undesirable.

RESULTS

Series I. In the first series, a base line was sought by using a small series (28 dogs) of animals and by conducting the adhesion count at frequent intervals, ranging from 1 day to 21 days. It was hoped that by this means a rough estimate of tissue tolerance and rate of absorption of the powders could be obtained. It was not expected that this series would be statistically significant, but only that it would aid in determining at what intervals a larger series of animals might most profitably be studied. The results of this series of experiments are summarized in Table I.

No valid conclusion can be drawn from this series. In a few instances, where the interval between implantation and adhesion count coincided with the intervals in the first series, the same animal was included in the second series, since this increased the statistical sampling without vitiating the results in either series.

TABLE I.—SERIES I (28 DOGS)

Test material	Average number of adhesions			
	1–2 days	3–7 days	8–15 days	16–21 days
Starch+MgO (2%)	14 (2)	12 (2)	10 (3)	4 (4)
Starch+$MgCO_3$ (3%)	9 (2)	11 (3)	5 (3)	4 (6)
Control (No powder)	—	—	—	2 (2)

The small figure in the upper right corner indicates the number of dogs from which the average adhesion count was obtained.

Series II. In the second series, 66 animals were evaluated. Of these, 17 were examined after 2 days, 30 after 18 days, and 19 after 25 days. The statistical results are summarized in Table II.

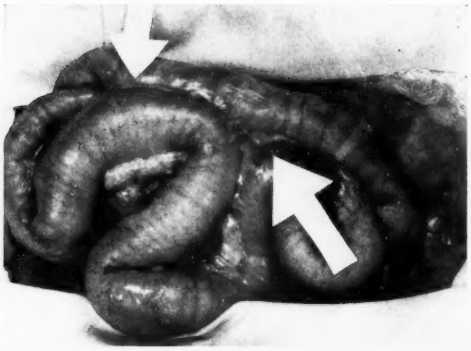
It is seen from this table, that even with a relatively large dose of powder, adhesion formation is not extensive, regardless of which dispersal agent is used. In comparison with talcum powder, as demonstrated in our own and other previous studies, the reaction is not severe, but there is nevertheless *enough reaction to merit serious consideration and a conscientious effort to avoid it.* The rather wide range in the number of adhesions reflects the introduction of variables such as subclinical infection, health of the animal, uneven application of test powder, and variations in the degree of trauma during operation, as outlined in the preliminary discussion.

It was pointed out previously that in an empirical, and therefore necessarily inaccurate study of this kind, with many uncontrolled variables, numerical comparison alone is likely to convey a distorted impression. In the accompanying illustrations, representative examples of the gross and microscopic results are

TABLE II.—SERIES II (66 DOGS)

Interval from implantation until adhesion count, days	Starch with MgO			Starch with $MgCO_3$			Control—No powder		
	Greatest No. of adhesions	Smallest No. of adhesions	Average No. of adhesions	Greatest No. of adhesions	Smallest No. of adhesions	Average No. of adhesions	Greatest No. of adhesions	Smallest No. of adhesions	Average No. of adhesions
2	22	5	10.5 (9)	19	4	13.8 (6)	0	0	0 (2)
18	34	0	9.9 (11)	22	0	10.7 (11)	1	0	.33 (3)
25	10	2	5.1 (7)	13	0	6.2 (5)	5	1	2.2 (4)

The small figure in the upper right corner indicates the number of dogs from which the average adhesion count was obtained.



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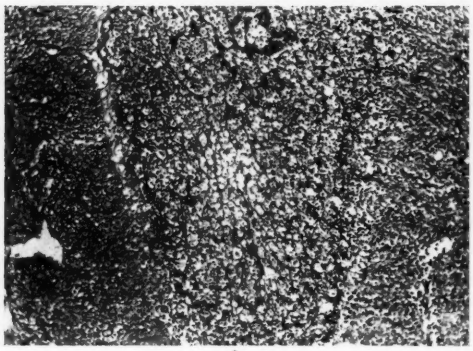

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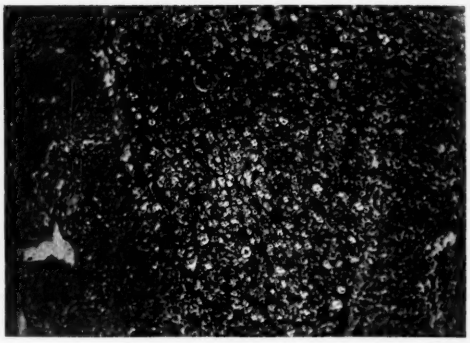

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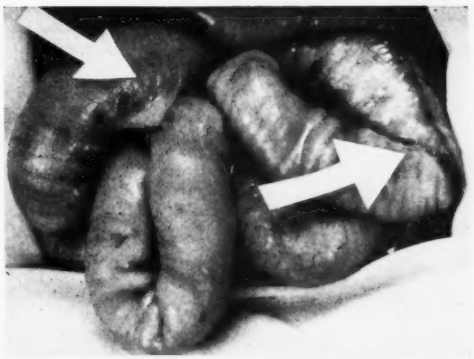
Fig. 1. Dog 877. Starch powder with 2 per cent magnesium oxide—24 hours. a, Gross appearance of the bowel. The serosa is dull and lusterless, as it appeared immediately after dusting. Adhesion count—14. b, Section through an adhesion as seen under ordinary illumination. ×75. c, The same field as that shown in b, with partial rotation of the polarizing discs. The adhesion is seen to consist of acute inflammatory exudate interspersed in which are numerous starch granules.

presented which will help to clarify the interpretation.

Figures 1 and 2 indicate the typical appearance of the dog's bowel 24 hours after implantation of the test powders. The reaction is almost identical, regardless of which dispersal agent has been used with the starch powder. The serosal surface of the bowel is dull and lusterless, as it looks immediately after the powder is applied, but no adhesions have formed where the distribution of powder is even and where it has separated into individual granules. Adhesions did develop wherever clumps of powder had fallen. Here, under the microscope, a fresh fibrinopurulent exudate is seen with abundant polymorphonuclear leucocytes. Under polarized light, the mass of starch granules is readily seen. The gross adhesion count appears to reflect the number of such clumps or aggregates of powder granules rather than a general inflammatory reaction such as is seen in bacterial peritonitis. Hence at this early stage, a foreign body reaction to aggregate masses of powder granules seems to dominate the picture, and the total adhesion count of 14 and 28 is not actually significant.

In Figures 3 and 4, the situation after 8 days is shown. Polymorphonuclear cells are less numerous, fibroblastic proliferation is present, and foreign body giant cells have appeared. A developing granuloma is now evident and starch granules are still present in large numbers. Except in the areas where these clumps of powder have fallen, a healthy peritoneal sheen is apparent and the serosa looks normal. Thus, where the powder has been well distributed in individual particles, all reaction seems to have subsided. Whether or not the existing adhesions will absorb would then depend on how large a clump of powder produced each one of them and on the indeterminate



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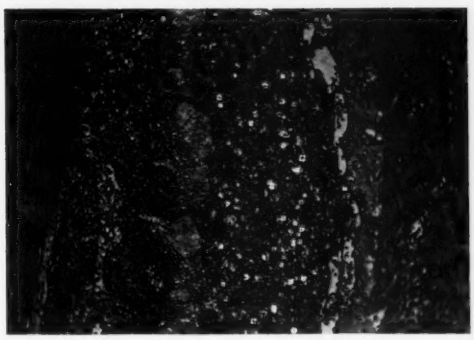

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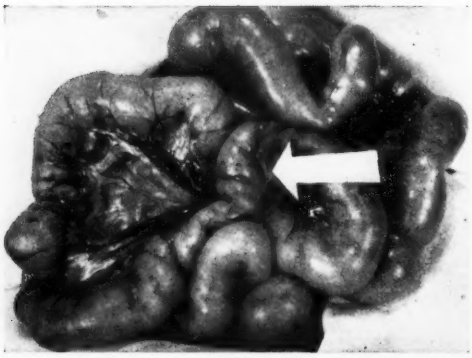
Fig. 2. Dog 34. Starch powder with 3 per cent magnesium carbonate—24 hours. a, Gross appearance of the bowel, which is similar to that of the animal in Figure 1. Adhesion count—21. b, Section through an adhesion, with ordinary illumination. ×75. c, The same field as that shown in b, with partial polarization of the light. ×75. The findings do not differ significantly from those shown in Figure 1.

factors of subclinical infection and other variables. There is no significant difference in the tissue response to the starch powder, regardless of which dispersal agent is used. The difference between 8 and 12 adhesions is, therefore, of no experimental importance so far as the two powders are concerned.

The next two groups of photographs illustrate the findings in 2 dogs in which adhesions were still present after 18 days. In Figure 5 (dog 99), 1 adhesion remains, while in Figure 6 (dog 88) there were 34 adhesions. In cold figures, this would suggest a wide difference in the reaction to the two dispersal agents. In both dogs, the bowel is normal except where the residual adhesions are present. This suggests that the adhesions have occurred where clumps of powder fell. It is reasonable to suppose that most of the clumps were small in dog 99 and the resulting granulomas did not develop into irreversible fibrous scars. When the starch was digested and absorbed, the granulomas disappeared. However, where a large clump fell, even though the starch was absorbed, the process took so long that a fibrous adhesion has remained, which is likely to be permanent. No starch is seen under polarized light and this illustration is, therefore, omitted. In Dog 88, although 34 adhesions are present, their appearance, both grossly and microscopically, suggests that they are very close to complete absorption. A few starch granules remain but there is little or no fibrous proliferation, and when compared with the 8 day dogs, it may be surmised that this dog's bowel would have been clean and free of adhesions in a few more days. The animal is actually much better off than the one who has only a single large adhesion of a permanent character. It is presumed that subclinical infection did not play a major part in the persistence of this single adhesion, because if this had been the



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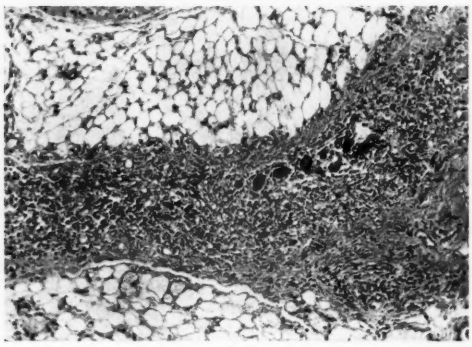

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Fig. 3. Dog 43. Starch powder with 2 per cent magnesium oxide—8 days. a, The bowel is clean and healthy looking except where there are adhesions. Adhesion count—12. b, Section through an adhesion, as seen under ordinary illumination. Polymorphonuclear infiltration is much less marked than it was in the 24 hour period but fibroblastic and capillary proliferation are evident. ×75. c, Under partially polarized light numerous starch granules are demonstrated. ×75.

case, it seems unlikely that the rest of the bowel could have returned so completely to normal. Thus the size of the clump of powder is believed to have been the determining factor.

Reference to Table II will show that dog 88, with his 34 adhesions, represented the animal with the greatest number of adhesions encountered after 18 days. The average number of adhesions in 27 dogs was 9.9, and most of the animals had no adhesions, as shown in Figure 7, a and b. Their bowel surfaces were usually as clean as were those in the control animals (Fig. 7c). It may be concluded then that unless large powder clumps or masses are present, the adhesions initially formed are absorbed when the starch powder is absorbed, provided ideal conditions of atraumatic and aseptic handling exist.

If infection supervenes, the reaction will certainly be much more violent, and even though the starch, like surgical catgut, is ultimately absorbed, permanent scarring and unabsorbable adhesions may be expected. This situation is exemplified in Figure 8. In this animal, a gross wound infection indicated that asepsis had not been achieved at the initial operation. Twelve days following implantation the entire bowel was fused in a mass of uncountable adhesions, and microscopic section showed not only the starch granules but also a persistently severe inflammatory reaction. This, of course, represents the result of gross bacterial contamination. Somewhere between this extreme and the complete absence of persistent reaction, shown in Figure 7, will lie the effect of starch powder on a peritoneum in which subclinical infection is present. This is a phase of the problem which defies accurate analytical study.

When an interval of 25 days elapsed between implantation and re-examination, the average adhesion count dropped appreciably,

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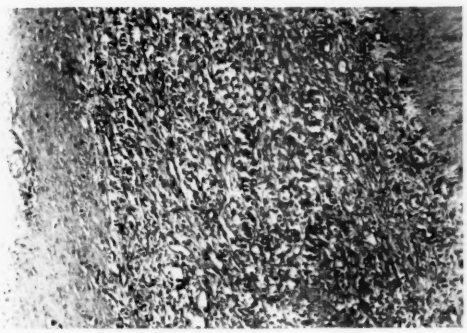

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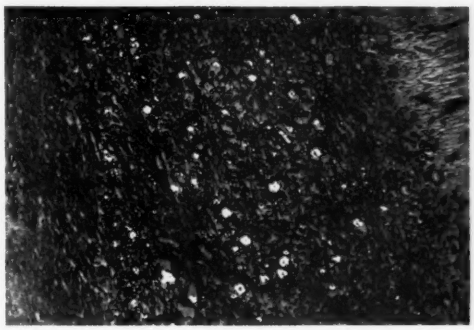

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Fig. 4. Dog 55. Starch powder with 3 per cent magnesium carbonate—8 days. a, Gross appearance of the bowel. The serosal surfaces appear normal except where clumps of powder have fallen. Adhesion count—8. b, Under ordinary illumination the inflammatory process is similar to that seen in Figure 3, except for the absence of foreign body giant cells. ×75. c, Under partially polarized light starch granules are abundantly present. The gross and microscopic findings are again essentially the same in both 8 day dogs.

suggesting that some of the adhesions produced by powder aggregates were not irreversible and were still capable of absorption. This outcome would seem to depend on both the size of the clump and on the uncontrolled variables. Under average conditions, as long as it is well dispersed, the powder is well tolerated and quickly and harmlessly absorbed. At both 18 and 25 days, most of the animals showed no adhesions, and in those in which adhesions persisted, the surfaces were clean except where large clumps had fallen. That the powder alone could not be held entirely responsible is illustrated by the fact that in the control animals a few adhesions occurred.

Study of sections made from the mesenteric nodes of the test animals showed a complete absence of any starch granules. This fact tends to confirm the observation noted in our previous report that powder particles on the peritoneum are either absorbed or encapsulated where they fall and are not taken up by the lymphatics.

DISCUSSION

Talcum powder was not used in the present study because its use would have represented a repetition of our own previous experiments and those of many other investigators. It has been established that talcum powder, applied under the conditions of these experiments, consistently produced a violent reaction with uncountable dense adhesions. The present work is not designed to demonstrate the superior safety of starch powder as compared with talcum powder. The dangers attendant upon the use of talcum powder as a glove powder have been abundantly demonstrated by many competent studies and are beyond question. Starch derivative powder has been shown, on equally good evidence, to be much better tolerated and to be as nearly innocuous as it is possible for any sterilizable powder to

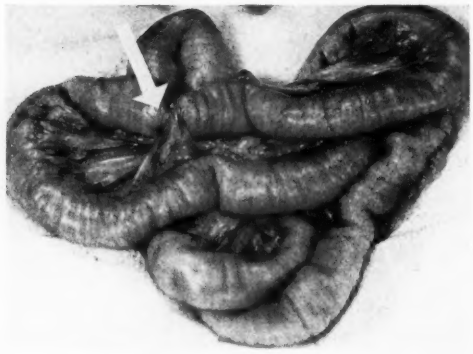

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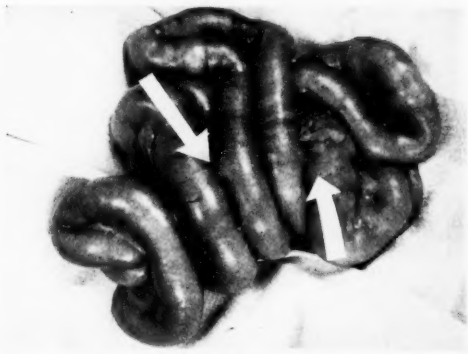
Fig. 5.



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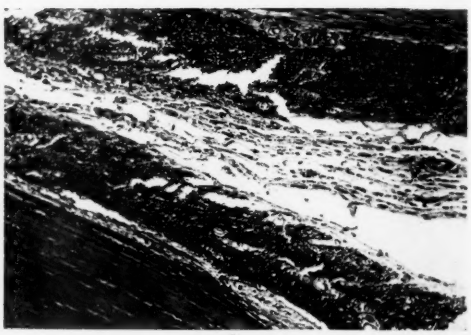


b

c

Fig. 6.

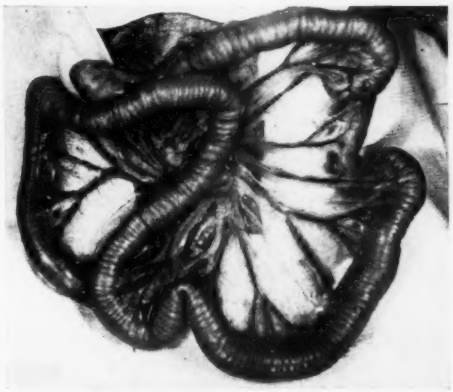
Fig. 5. Dog 99. Starch powder with 2 per cent magnesium oxide—18 days. a, Gross appearance of the bowel. The serosal surfaces appear normal except for a single adhesion. b, Section through the adhesion. A firm fibrous scar is present. c, Under polarized light no starch was demonstrated and is, therefore, not illustrated. ×75.

Fig. 6. Dog 88. Starch powder with 3 per cent magnesium carbonate—18 days. a, The bowel appears healthy except for multiple small friable adhesions. Adhesion count —34. b, Under ordinary illumination a section through one of these adhesions demonstrates its tenuous character. Only a few starch granules are shown (c) to remain when the light is partially polarized. It is believed that such adhesions would progress to complete absorption in a few more days. ×75.

be. No matter how benign a powder may be, and no matter how quickly it is absorbed, it is, *for the duration of its presence in tissue*, a foreign body.

The present study has sought to emphasize this important point. The evidence presented indicates that starch powder is well tolerated provided it is properly dispersed into individual granules. The need for a dispersal agent in any starch glove powder is apparent from the results here presented.

Although a review of the extensive literature on the subject would not be worth while here, it is important to remember that the



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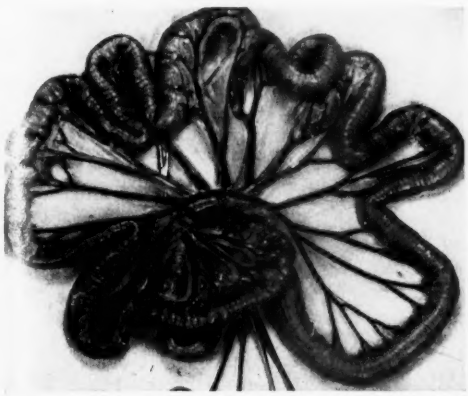

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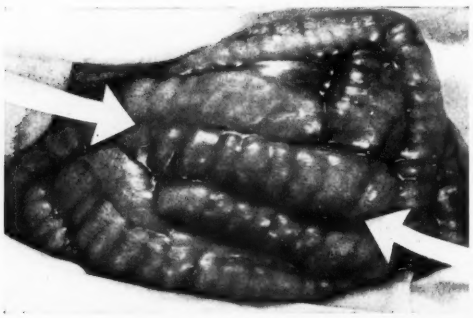
Fig. 7. a, Dog 319. Starch powder with 2 per cent magnesium oxide—18 days. No adhesions. b, Dog 86. Starch powder with 3 per cent magnesium carbonate—18 days. No adhesions. c, Dog 326. Control. No powder used. No adhesions. In general, if the powder was evenly distributed and no clumps or large aggregates were allowed to fall in any given area, absorption was complete in 18 days and no adhesions were formed.

"ideal" glove powder must meet a complex array of minimum requirements. Its physical qualities as a lubricant, its effect on the surgeon's hands, its effect on rubber gloves, and the tissue reaction when it contaminates a wound are all essential considerations. An absorbable, digestible, chemically inert powder such as starch was long recognized as approaching this ideal. The difficulty lay in achieving a sterilizable form of such a powder. The powder derived from polishing raw rice, for example, is finely divided and chemically benign and has been used for centuries in the Orient for cosmetic purposes. But it cannot be sterilized without loss of all its desirable properties as a glove lubricant. The same difficulty applied to other vegetable powders until a method could be found to harden or tan their individual whole granules in order to make them resistant to autoclaving. An early approach was to fix the granules with formalin, but this procedure immediately introduced a strong chemical which living tissue could not tolerate. The "tanning" process mentioned earlier accomplishes the desired result effectively in corn starch, but to assure further the adequate dispersal of the particles, a dispersal agent is added. There appears to be no significant difference, so far as tissue tolerance is concerned, between 2 per cent magnesium oxide and 3 per cent magnesium carbonate as dispersal agents.

The present study indicates that this dispersal into individual granules is essential to



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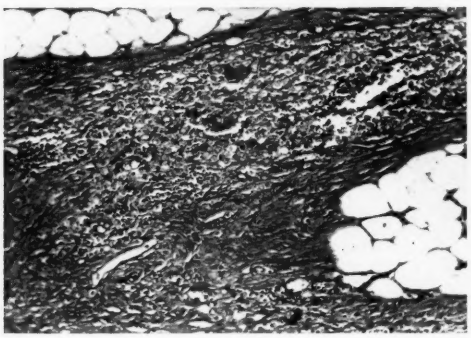

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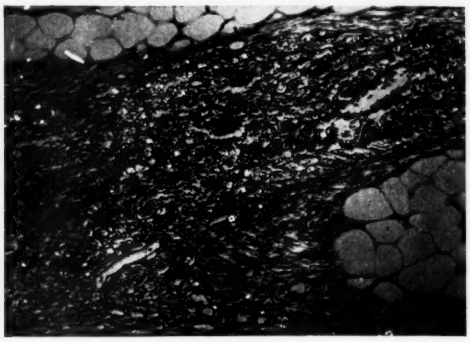

c

Fig. 8. Dog 77. Starch with 3 per cent magnesium carbonate—12 days. A gross wound infection occurred and obvious bacterial peritonitis was present. The entire bowel is fused by adhesions in which a violent inflammatory reaction is seen microscopically. These findings, in the presence of infection, after 12 days, may be compared with those after 8 and 18 days in which no demonstrable infection occurred. ×75.

rapid absorption and to minimum reaction in tissue. The starch powder used in these experiments is so finely dispersed after autoclaving, that a number of surgeons have complained that it clouds the air too much when they put their gloves on. In terms of tissue tolerance, this dispersal is highly desirable but it emphasizes one of the precautions which should be taken in using any powder lubricant for gloves.

Although the conditions of these experiments and the quantities of powder used represent a much more rigorous test than ordinarily would be encountered in clinical practice, the results are representative of what may occur when the powder is permitted to contaminate surgical wounds. Clumps of powder can gain access either from heavily powdered glove surfaces or when a glove is accidentally torn or punctured at the finger tips. It is obvious that in clinical practice the bowel would not be dusted heavily with powder as it was in these studies. The fact that the reaction is relatively slight, even under these conditions, is an indication of the desirable qualities of treated starch as a glove powder. More important, however, is the clear implication that this or any other powder is not foolproof. If it is carelessly used, especially in the presence of infection or any of the other variables which are consistently present in clinical surgery, it can produce adhesions which may not be absorbed.

The same precautions which were employed when talcum powder was in general use are still important when starch powder is used. The fact that starch powder is biologically "nonirritating" and absorbable, when finely dispersed, does not mean that the basic surgical principles of avoiding contamination of wounds with foreign material may be abandoned. Air contamination should be kept at a minimum and gloves should be thoroughly washed as free of powder as possible before the operation is begun. If a glove is torn or punctured, it should immediately be replaced and

the fresh glove should be washed before the wearer returns to the surgical field.

This is not to say that starch powder is any less safe, in comparison with talcum or lycopodium powder, than the original studies indicated. We believe that treated starch comes as close to being an ideal glove powder as is theoretically possible. The point is that as long as powder is used as a glove lubricant (and its advantages over the old "wet technique" are obvious), due precaution should be taken to avoid contamination of the wound with the lubricating powder. The preventable hazards inherent in mineral or chemically irritating powders have been eliminated, but the principles of foreign body reaction remain and must be given due consideration.

CONCLUSIONS

1. Although treated starch powder is biologically absorbable in tissue, it produces a foreign body reaction as long as it is present.

2. The intensity, duration, and reversibility of the foreign body reaction produced by starch granules is influenced by many variables, of which some can be controlled and some cannot.

3. The complete dispersal of the powder into individual granules is essential and is one of the controllable variables. When adhesions are produced by starch powder, they appear to be the result of "clumps" or aggregate deposits which cannot be absorbed as rapidly as can the individual granules. The longer absorption is delayed, the greater is the likelihood that the foreign body reaction will be irreversible and that the adhesions will be permanent. In the absence of infection and under ideal conditions, a large dose of starch powder appears to be relatively harmless to the peritoneum provided it is properly dispersed into individual particles which can be absorbed quickly.

4. There appears to be no difference in the tolerance of the peritoneum to treated starch powder, regardless of whether 2 per cent magnesium oxide or 3 per cent magnesium carbonate is used as a dispersal agent.

5. Sterilizable corn starch approaches the theoretical ideal as a powder lubricant for gloves. Nevertheless, any powder, no matter how benign it may be or how quickly it is absorbed *produces some degree of foreign body reaction when it contaminates an open wound.*

6. Every possible precaution should be taken to prevent powder contamination of open wounds or serosal surfaces, and no powder is so "safe" that it can be carelessly used.

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INDICATIONS FOR COLOSTOMY IN PATIENTS WITH HIRSCHSPRUNG'S DISEASE

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DURING our initial experience with the surgical treatment of Hirschsprung's disease a three stage operation was used (3). First, a transverse colostomy was made. Second, after a period of several months a part of the aganglionic bowel was resected during the abdominal part of the operation. The remaining rectal stump was turned inside out and the proximal bowel pulled through. In this manner it was possible to make the anastomosis in an easily accessible position outside the perineum. After the anastomosis was completed the bowel retracted into the pelvic cavity and the suture line was adjacent to the insertion of the levators. At a third operation several weeks later the colostomy was closed (Fig. 1). The first 5 patients in our series were treated according to this program. Subsequently, colostomy was dispensed with in most instances and the procedure reduced to a primary resection without any disadvantage to the patient (2). There have been uniformly good postoperative results in both the group treated with the multiple stage operation and the group treated with primary operation. This report is based on a study of 70 patients who have been followed for from 1 to 5 years.

During the past year we have resected the aganglionic rectosigmoid and rectum in 30 patients with Hirschsprung's disease, and of these only 2 had preliminary colostomy. In both instances the reason for colostomy was a special problem presented by the patient and not a protection for the subsequent resection and anastomosis. We now have two indications for colostomy: (1) in patients with almost complete large bowel obstruction whose distention cannot be controlled and reduced by colonic irrigation, and (2) in patients whose extremely poor condition makes primary resection a hazardous procedure.

There are three disadvantages to the use of our original multiple stage operation. (1) Three separate operations are required. (2) After a few months the defunctionalized distal colon becomes small in caliber. Later, when resection of the rectum and rectosigmoid is performed the stoma at the suture line is considerably smaller than the normal bowel lumen. As the colon begins to function, dilatation to normal size occurs and a relative stricture exists at the suture line. (3) The normal bowel distal to the colostomy may be too short to reach the perineum, which makes it difficult or impossible to perform anastomosis to the anal cuff.

A recent patient illustrates this particular disadvantage of transverse colostomy. At operation, the aganglionic bowel extended to the splenic flexure, and the bowel from the colostomy to the lesion was not sufficient to reach to the perineum. Neither was the colon from the cecum to the colostomy of sufficient length for the reconstruction. Consequently, the colostomy had to be closed and a new one made in the region of the splenic flexure. By utilizing all the colon from the cecum to the splenic flexure reconstruction will be possible at a subsequent operation.

Potts has reported that some infants and children with transverse colostomy have suffered from life endangering fluid loss from the colostomy. None of our group of 24 patients on whom we performed transverse colostomy or ileostomy has presented such a problem of fluid loss. They all gained weight within the range of a normal child of their age.

At the present time a patient with Hirschsprung's disease who requires proximal decompression is treated by performing a sigmoid colostomy. The opening must be made in the dilated and hypertrophied colon and not

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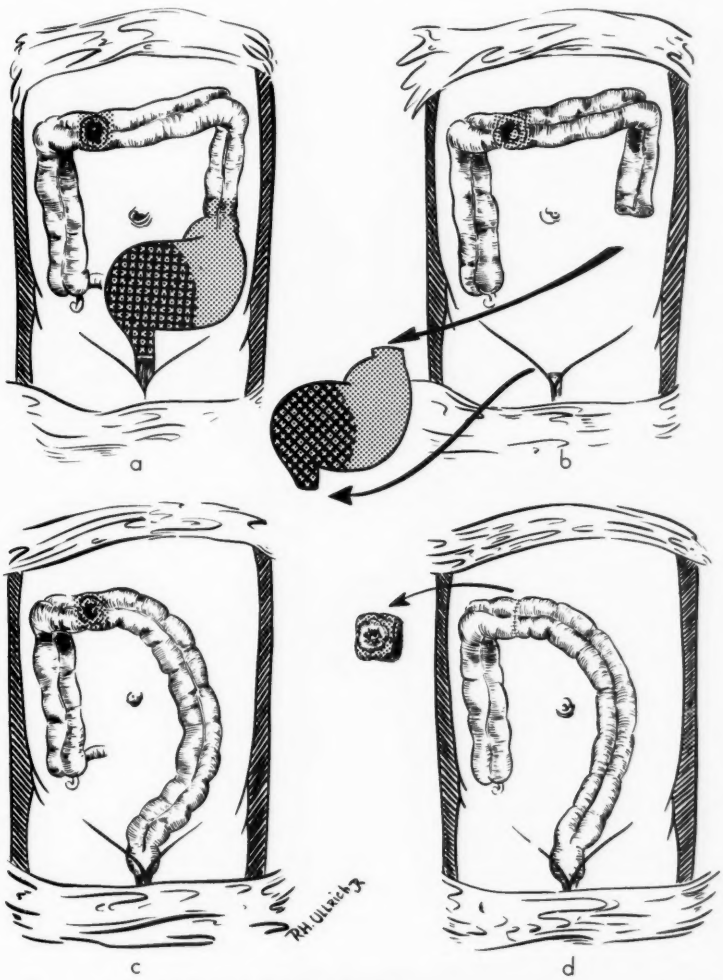

Fig. 1. a, In the original multiple stage procedure a transverse colostomy was the first operation. b, c, Resection of the aganglionic rectum and rectosigmoid was the second operation. d, The third stage was closure of the colostomy.

in the narrow, aganglionic bowel. A small piece of colon wall down to the mucosa should be removed at the proposed level of the colostomy and examined immediately for ganglion cells to assure placing the colostomy in normally innervated intestine. When the patient is ready for resection some months later, the colostomy is detached from the abdominal wall and is removed with the distal aganglionic colon. An anastomosis is performed between the lower rectum and the colon proximal to the colostomy (Fig. 2).

With this plan two operations are required and considerable expense and time are saved the patient. Furthermore, the bowel above the colostomy is normal in size assuring an adequate stoma at the anastomosis. Lastly, there is no fixation of the transverse colon by a

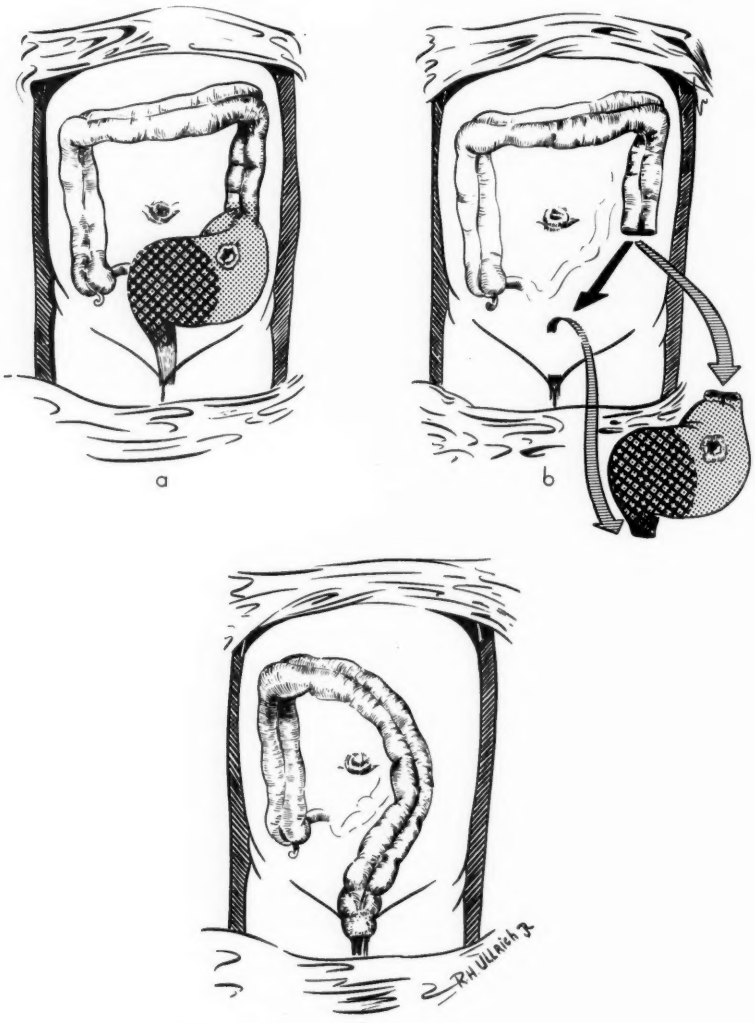

Fig. 2. a, Our routine now calls for colostomy in the sigmoid or descending colon. b, c, The second and last stage is resection of the aganglionic bowel including the colostomy.

colostomy to limit the proximal line of resection.

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THE BRONCHIAL ARTERIES AND THEIR CONNECTIONS WITH OTHER VESSELS IN THE HUMAN LUNG

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THE bronchial arteries in the human lung are usually considered to be the main blood supply to the bronchi as far peripherally as the respiratory bronchioles, and at this site, to connect with branches of the pulmonary vessels by means of capillaries. However, it has been suggested that the bronchial and pulmonary arteries normally anastomose by means of vessels larger than capillaries. In addition to supplying the bronchi, the bronchial arteries have also been described as supplying certain areas of the visceral pleura, the tracheobronchial lymph nodes, and the midportion of the esophagus. Bronchial veins draining the intrapulmonic bronchi empty into the pulmonary veins; those draining the extrapulmonic course of the bronchi empty into the azygos system.

In certain pathologic conditions, vessels larger than capillaries are known to connect the bronchial and pulmonary arteries; the bronchial arteries together with these connections may then enlarge sufficiently to take over part or all of the function of the peripheral branches of the pulmonary artery. If there should be partial obstruction of the pulmonic venous flow, the bronchial veins may help to return part of the blood from the lungs to the right side of the heart by way of their connections with the azygos system and the vena cava.

A knowledge of the embryology of the bronchial vessels and their connections with the pulmonary vessels would be of help in ascertaining whether or not communications normally exist between these two systems of vessels during development, and whether these remain during the subsequent period of growth, to become functional channels in later life.

The studies presented here were undertaken to acquire further information on the embryologic origin of the bronchial arteries, their course and anastomoses with the pulmonary artery in the fetus, child, and adult, and their relationship to the other pulmonary vessels in normal and pathologic lungs.

MATERIALS AND METHODS

Since, to the knowledge of the author, no specific study had been made on the embryology of the bronchial vessels in human embryos, although suggestions as to their possible development are presented in standard anatomical texts, a study of this problem was undertaken using serially sectioned human embryos varying in age from the 4th through 7th week.[1] Sections of isolated lungs from uninjected fetuses, or fetuses injected with solutions of India ink, colored gelatin, liquid latex, or vinyl acetate were also used.[2] These fetuses ranged in age from the second through the ninth month of gestation and were selected at approximately weekly age intervals. In addition, studies were made of vascular casts obtained by injecting the pulmonary vessels with different colors of vinyl acetate or liquid latex. After obtaining sample sections from certain areas of these injected lungs for histologic study, they were either macerated in concentrated hydrochloric acid (after vinyl acetate injection) to remove the pulmonary tissue, or they were embalmed and dissected to follow the course of the vessels (after liquid latex injection). Utilizing these methods, 52 lungs obtained at autopsy or surgery, from patients varying in age from a few days to 91 years were studied. The bronchial arteries were injected with a specific colored solution in 25 of these 52 specimens and, in a

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[1]The serially sectioned embryos used for this study were 3.0, 4.6, 5.0, 6.0, 8.0, 10.0, 17.0, 20.0, and 25.0 mm. CRL. respectively.

[2]The source of the liquid latex and the vinyl acetate as well as the technical procedures involved in their use have been described by Tobin and Zariquiey (1950).

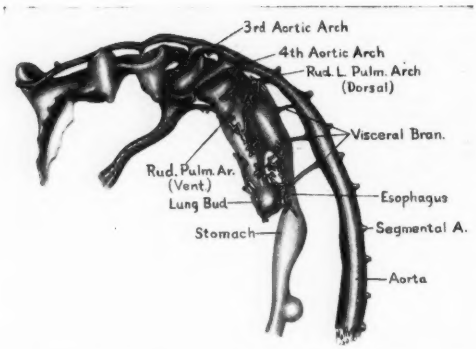


Fig. 1. Diagram (modified from Congdon) of the arterial supply to the region of the developing esophagus, trachea and lung buds based on the study of sections from a 5 millimeter CRL embryo. Note that visceral, segmental branches of the dorsal aortas and the early primordia of the pulmonary artery supply this region. Visceral branches, not shown, would also supply the region of the developing stomach and duodenum.

few instances, the respiratory passages were also injected with a solution of a different color from that used for the vessels. Normal as well as pathologic lungs were used to study the course of the vessels and their changes in certain pathologic conditions.

OBSERVATIONS

Bronchial-pulmonary arterial anastomoses. Embryos.—Studies of the sectioned embryos indicate that during the fourth week of gestation the developing lungs, trachea, and esophagus are supplied by branches from the paired dorsal aortas which form a capillary plexus around these structures. This plexus is drained by vessels connected with the anterior cardinal veins. The earliest blood supply to the region of the developing lungs therefore is associated with the systemic circulation. Additional arterial branches are also derived from the developing fourth aortic arch and the aortic sac as these structures are formed, as shown by Congdon (1922), and others (Fig. 1).

Later with the formation of the pulmonary arteries and veins (Fig. 2), these vessels also connect with the capillary plexus around the developing lungs and potential channels for anastomoses between the bronchial and pulmonary vessels are established. The youngest specimens available for injection were in the 7 to 8 week group, and in these embryos the course of the bronchial arteries could be definitely established. At 8 weeks, the vascular channels of the lung, as in other parts of the body, are assuming their definitive form. Later, with the growth of the lungs and trachea and their shift to a more caudal position in the body, the bronchial arteries were observed to arise from the aorta on the left side, and from the subclavian, the highest intercostals, or the internal mammary on the right side.

Therefore, as in the case of other viscera, the blood supply to the developing lungs at first consists of a series of small segmentally arranged branches from the unpaired, and later from the paired, dorsal aortas. With growth and change in position of the lungs, some of the craniad blood vessels atrophy, while others to this tissue are formed further caudad, until the definitive branches develop which will become the main arteries. Since the right and left ventricles of the fetal heart are approximately the same size and produce about equal pressures, the pulmonary arteries carry more blood, normally become larger, and assume a greater role in supplying the developing lung tissue than the bronchial arteries; which are smaller, carry less blood, and develop at a much slower rate. However, as shown in a subsequent section of this paper and previously reported by others, in congenital pulmonary stenosis the bronchial arteries may remain as comparatively large channels and may carry sufficient blood to maintain fairly normal growth of the lung as well as take care of a good part of the respiratory function.

Child and adult.—Anastomoses between bronchial and pulmonary arteries were found in 25 specimens in which the bronchial arteries were specifically injected, and in 4 others in which they were retrogradely filled from the pulmonary arteries. In other specimens, anastomoses could not be definitely identified. These anastomoses were of two types: one type was relatively short (1 to 2 mm.) and narrow (50 to 100 micra), resembling those described by von Hayek, Verloop, and Lapp; whereas the other type was long (10 to 40 mm.)

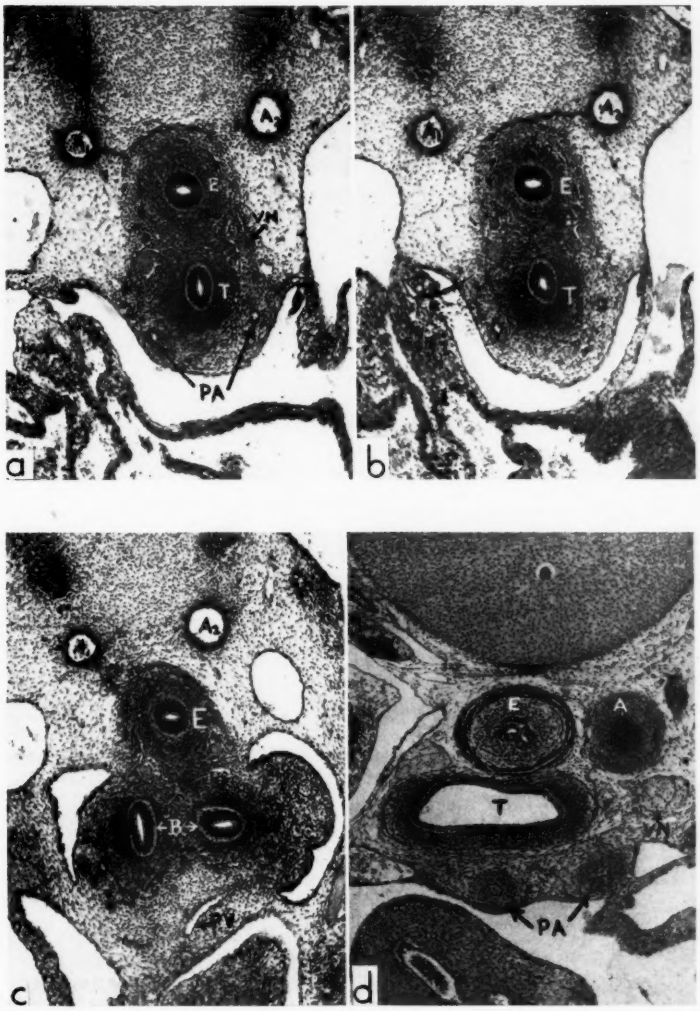
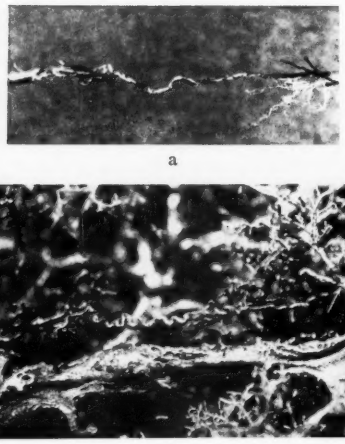


Fig. 2. Photomicrographs of transverse sections through the region of the developing esophagus, trachea, and bronchi of 10 millimeter (a–c) and 19.5 millimeter (d) CRL embryos. ×50. a, A branch from the left dorsal aorta (A_1), supplied the esophagus (E), vagus nerve (VN), and the trachea (T). The size and location of the developing pulmonary arteries (PA) are indicated. b, More caudad section showing a branch of the right dorsal aorta (A_2) supplying the tissues in this area. c, Further caudad section showing the two primitive bronchi (B) and another visceral branch of the left dorsal aorta (A_1) supplying the tissues in the region of the developing lungs. The size of a branch of the pulmonary vein (PV) is shown. d, A transverse section through the region of the developing esophagus (E) and trachea (T) of a 19.5 millimeter CRL embryo. At this age the definitive blood vessels are forming. Note the presence of a bronchial artery, derived from the aorta (A) coursing to the right side of the trachea (T). The size and location of the pulmonary arteries (PA) and vagus nerve (VN) are shown. ×50.



a

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Fig. 3. a, Photograph of an anastomosis between a branch of the pulmonary artery (black) and bronchial artery (white) from vinyl acetate casts of these vessels injected with red and yellow colored solutions of this plastic, respectively. This anastomosis was from vascular casts of the pulmonary vessels of a 49 year old male who had generalized hypertension, coronary insufficiency, and pulmonary edema. ×13. b, Photograph of the vinyl acetate cast of a coiled bronchial artery retrogradely filled from the pulmonary artery. Note the cast of the large pulmonary artery coursing transversely across the lower part of the figure. The coiled artery originated from a small branch of the pulmonary artery, indicated by the arrow, and coursed in the wall of a bronchus parallel to the pulmonary artery. This specimen was obtained from the lung of a 69 year old female who had hypertension, bronchopneumonia, and pyelonephritis. ×11.

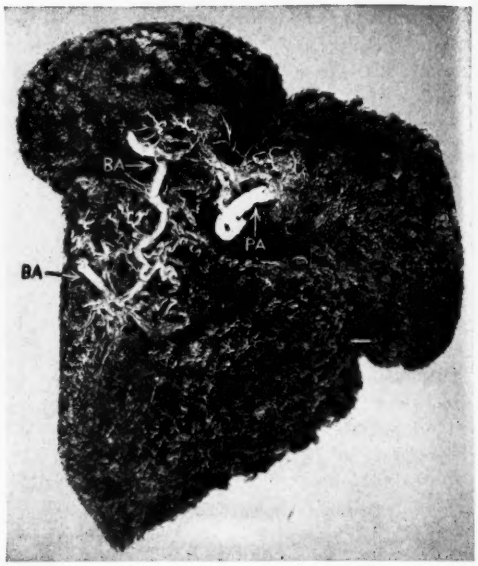

Fig. 4. Photograph, mediastinal view, of the vascular casts from the left lung of a 4 year old boy who had bouts of cyanosis, congenital absence of the right ventricle, a patent foramen ovale but an occluded ductus arteriosus. This patient died the day following the performance of a "Blalock operation." Injection of the vessels demonstrated the presence of many bronchial arteries (*BA*) from the aorta supplying the lung tissue and pleura. These arteries were seen to have anastomosed with branches of the pulmonary artery (*PA*) and retrogradely to have filled them. ×½.

and much wider (300 to 400 micra).[1] In both instances the arteries were coiled. The short type was located within the lobular subdivision of the lungs, whereas the longer anastomoses (Fig. 3) extended between a branch of the bronchial artery on the wall of a segmental bronchus to a more distally placed branch of the pulmonary artery. These larger branches were not found on every bronchus, but one or two were found in each bronchopulmonary segment.

These vessels were found in the lungs from the newborn, the child, and the adult up to 91 years of age, with different causes of death and with or without pulmonic pathology, provided a small amount of postmortem pulmonary edema can be interpreted as a normal and not a pathologic finding. Since it is difficult to inject and see the bronchial arteries, even by cinefluorography, in the normal, living lung, it is not known whether there are anastomoses larger than capillaries found in such lungs. However the two most normal specimens in this series were from a 15 year old boy who died shortly after operation for a temporal lobe tumor and one from a 17 year old boy who died the day following cerebral contusion from an automobile accident. In both cases the anastomoses were observed but some pulmonary edema was present.

The coiled nature of these anastomoses may be due to the spiral musculature in their walls, which must act as sphincters for the anasto-

[1]These measurements were made after the vinyl acetate had hardened in the vascular lumina and the lung tissue had been mascerated and removed from the vascular casts. The original lumina of these vessels were probably 50 to 75 per cent larger than these measurements, due to the shrinkage of this injection medium.

motic channels and their being associated with a distensible tissue and hence subjected to stretch. According to Reynolds (1948), the coiled structure would reduce the pressure (from the bronchial to the pulmonary artery) by distance which the blood would have to traverse per unit of vessel, the decrease in size of the vessel, and the increased friction of the blood along the coiled walls.

As an indication of the role of these anastomoses in certain pathologic conditions, two examples will be cited. The first concerns one of 3 cases of stenosis of the pulmonary artery studied. In a 4 year old boy, who had cyanosis since birth, cinefluorography indicated that the lungs were supplied by a group of diffuse vessels originating from the aorta and that only one ventricle was present. The "Blalock operation" was performed on this boy who died shortly postoperatively from an embolism in the right lung. At autopsy the right ventricle was absent. Both atria were normal, the foramen ovale was open and the ductus arteriosus closed. The pulmonary conus was of normal size but it had no communication with the single ventricle. The aorta and both lungs were obtained and injections of vinyl acetate were made into the pulmonary conus, pulmonary veins and the aorta to ascertain the course of the pulmonary vessels. The casts of this specimen showed that the lungs were supplied by numerous bronchial arteries originating from the aorta. These supplied the pulmonary tissue and, by anastomoses with branches of the pulmonary artery, retrogradely filled the pulmonary artery and conus (Fig. 4). This case illustrates that the early blood supply to the lungs from the aorta may remain as their supply in later life. That part of the pulmonary artery derived from the original conus arteriosus may also remain patent although in this case, it had no connection with the ventricle. Many other cases have been cited in the literature showing that the bronchial arteries may be the only source of blood to the lungs, either as the result of a congenital malformation or experimental occlusion of the pulmonary arteries.

The second example is from a 40 year old woman, who had hemoptysis over a period of years, bronchiectasis, and negative sputum,

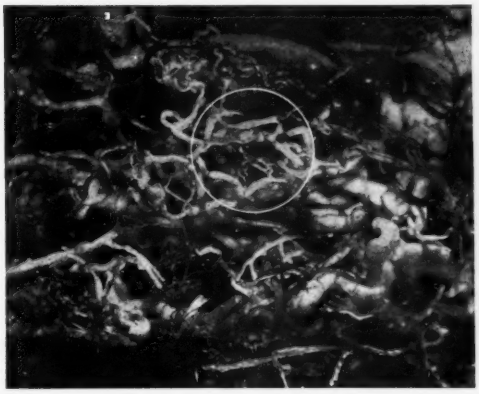

Fig. 5. Vascular casts from the bronchial arteries (white) and pulmonary artery (black) from a 40 year old woman who had bouts of hemoptysis, bronchiectasis, and an anteriovenous aneurysm in the right lung. Note the enlarged, coiled bronchial arteries and their anastomoses with branches of the pulmonary artery (encircled in white and in other parts of this figure). ×4. Compare with Figure 8 for the normal course of the vascular casts of the bronchial arteries.

although she was suspected of having tuberculosis. Cinefluorography as well as clinical examination led to the diagnosis of arteriovenous aneurysm. The right lung, removed at surgery, had multiple adhesions with collateral vessels arising from the internal mammary, intercostal, mediastinal, and diaphragmatic arteries, transversing the adhesions to enter the substance of the lung. Injection of the vessels in this lung revealed enlarged coiled branches of the bronchial arteries directly connected to the pulmonary artery (Fig. 5), and an enlarged arteriovenous aneurysm in the hilar region. Branches of the pulmonary artery also anastomosed with the arteries arising from the internal mammary and other systemic sources. In this instance, it appears that the increased pressure from the bronchial and the other collateral systemic vessels which anastomosed with the pulmonary artery may have raised the pressure within the pulmonary vein and resulted in the formation of the arteriovenous aneurysm; or a shunt between the pulmonary artery and vein may have enlarged under the increased pressure to produce the aneurysm. Such findings raise the questions of whether shunts larger than capillaries are normally found between branches of pul-

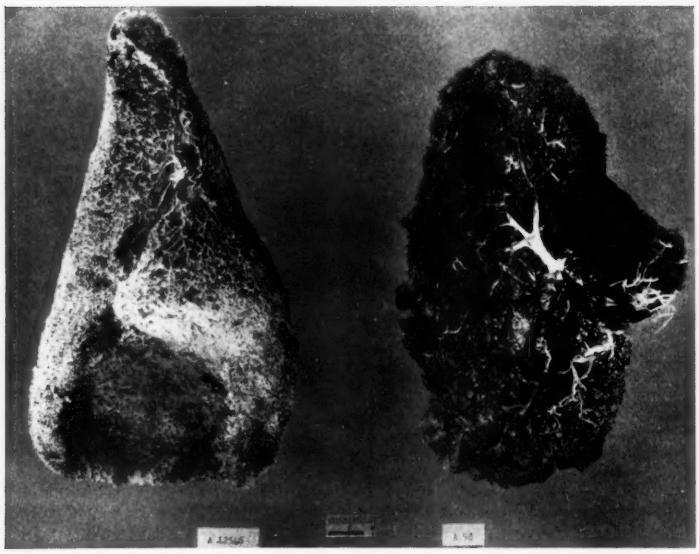

Fig. 6. Photograph of the vascular casts of the pulmonary artery (white) and pulmonary veins (black) from the left lung of a 17 year old male, who died of cerebral concussion (left) and that from a 13 year old female who had cyanosis since birth, a patent ductus arteriosus, and pulmonary hypertension (right). Note the normal filling of the branches of both the pulmonary artery and veins in the male's lung. In the female's lung, the branches of the pulmonary veins filled normally but only the larger branches of the pulmonary artery were filled by the injected vinyl acetate. ×½. See Figure 7 for a microscopic section from the female's right lung.

monary artery (and their connections with the bronchial arteries) and the pulmonary veins; and what might be the possible functions of these arteriovenous shunts in the normal adult or in the fetal lung.

Arteriovenous shunt. Although the question of paradoxical emboli is a puzzling one and many accounts have been given to explain this phenomenon including residual patency of the foramen ovale, Prinzmetal and associates (1948) have demonstrated arteriovenous shunts larger than capillaries in the lungs of certain animals and Tobin and Zariquiey (1950) have shown them to be present in the isolated lungs of infants and adults, which might be the channels that such emboli traverse.

Secondly, these shunts may play a role in the diversion of blood, away from parts of the fetal or adult lung not requiring a large circulation, or they may be instrumental in preventing increased pressure from causing hypertrophic changes in the walls of the pulmonary artery to result in pulmonary hypertension. Although the capacity of a vessel cannot be judged by its cross-sectional area with any degree of accuracy, the studies made by Patten and Toulmin (1930) indicate that there is little if any change in the cross-sectional areas of the pulmonary arteries and veins before and after an infant had breathed. This is further substantiated by the angiocardiographic studies of Lind and Wegelius, (1949) who used living human fetuses obtained by therapeutic abortions and found only slight filling of the distal branches of pulmonary vessels by the injected radiopaque material whereas small vessels in other organs were filled with this material. Assuming that capillary flow around the alveoli is not as large in the unexpanded as in the expanded lung, and in view of the observations of Civin and Edwards (1951), that the lumen of the smaller, muscular branches of the pulmonary

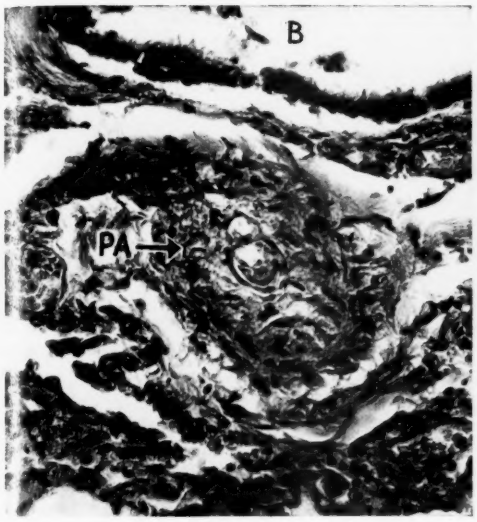

Fig. 7.

Fig. 7. Photomicrograph of a section through the right lung from the female whose left lung was injected and the vascular casts shown in Figure 6. Note the proliferation of the layers in the wall of the pulmonary artery (*PA*) subjacent to the bronchus (*B*). This proliferation in the walls of the pulmonary artery was associated with pulmonary hypertension and was probably due to increased pressure from the patent ductus arteriosus. ×71.

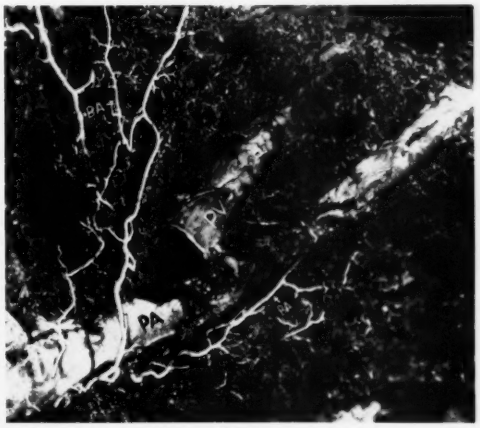

Fig. 8.

Fig. 8. Photograph of the vascular casts from the lung of a 49 year old male. Note the usual course of the bronchial arteries (*BA*). The course of a branch of the pulmonary artery (*PA*) and that of a branch of the pulmonary vein (*PV*) are shown. ×4.

artery are relatively narrower before than after breathing has occurred, and therefore would offer some resistance to pulmonary flow, these arteriovenous shunts perhaps are formed to direct some of the blood from the pulmonary artery, and their anastomoses with the bronchial artery, directly into the pulmonary veins and away from the unexpanded alveoli. This postulate is further suggested in the mature animal by Björk and Salén (1950), who have shown that there is no immediate, but only a gradual change in the size of the large pulmonary vessels, as judged by angiograms of dogs, with experimentally produced atelectasis. It is also well known that patent ductus arteriosus may lead to pulmonary hypertension in infancy, early childhood, or during adulthood as a result of hypertrophic changes in the walls of the smaller branches of the pulmonary arteries. Since the flow through the patent ductus, after birth, may be from the aorta to the pulmonary artery, and in this respect the pressure from the higher systemic to the lower pulmonic pressure systems would be comparable to that from enlarged bronchial arteries, it is interesting to speculate why all cases of patent ductus arteriosus do not show hypertrophic changes in the walls of the pulmonary arteries, resulting in pulmonary hypertension at an early age, or whether arteriovenous shunts may play a role in such cases. As examples, in a child with patent ductus arteriosus who developed pulmonary hypertension and changes in the walls of her pulmonary vessels (Figs. 6 and 7), no arteriovenous shunts were found in her lungs by injection techniques. However in a 36 year old male who had intermittent bouts of cyanosis, a short patent ductus was found at autopsy but no changes were observed in the walls of his pulmonary arteries. Arteriovenous shunts were demonstrated in the lungs from the latter case, both by the passage of glass spheres, many times the diameter of capillaries, from the pulmonary artery to and through the pulmonary veins and by the location of the shunts in the plastic casts of the pulmonary vessels.

It therefore seems feasible to assume that shunts between the pulmonary artery and pulmonary vein do normally exist, but their physiological function is not as yet under-

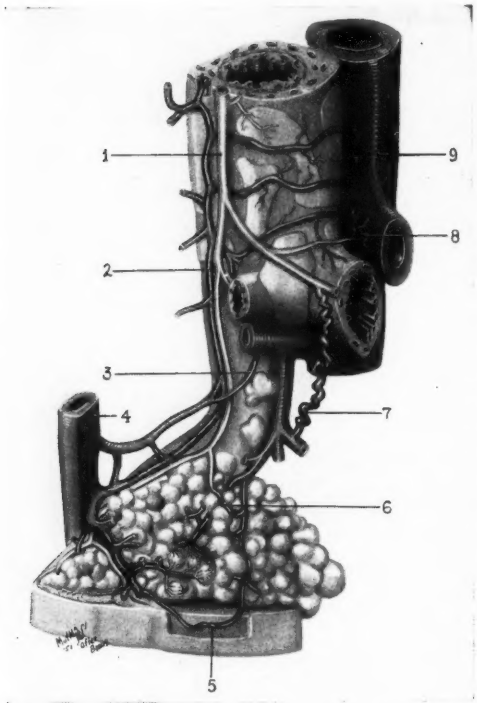

Fig. 9. Diagram (modified from Braus) showing some of the connections observed between the blood vessels in a smaller subdivision of the lung: *1*, bronchial artery; *2*, bronchial vein; *3*, shunt between a branch of the pulmonary artery and a branch of the pulmonary vein; *4*, intersegmental position of the pulmonary vein; *5*, shunt in the pleura between branches of the pulmonary artery and pulmonary vein; *6*, anastomosis between branches of the bronchial and pulmonary arteries in a lobule of the lung; *7*, longer, coiled anastomotic channel between branches of the bronchial and pulmonary arteries at the apex of the lobule; *8*, branch of the bronchial artery forming the vasa vasorum of the pulmonary artery; and *9*, a larger branch of the pulmonary artery coursing parallel to, and subdividing with, the branches of the bronchus. Also note a branch of the bronchial artery to the visceral pleura between adjacent segments (or lobules) at the lower left side of the diagram.

stood. Such shunts may be instrumental in regulating the flow of blood from the bronchial arteries, and their connections with the pulmonary arteries, or from a patent ductus arteriosus, to the pulmonary tissue or to the pulmonary vein.

Bronchial vessels. The variations in the origin and course of the bronchial arteries, described by Cauldwell and associates (1948) and others, were also observed in the present study. Each bronchus usually has two branches of the bronchial artery coursing along its length. These arteries may be straight in some areas or coiled and have several connections with other branches of the bronchial artery (Fig. 8) or with the pulmonary artery (Fig. 3). Although it is well known that bronchial veins drain both the deep and superficial parts of the bronchi, the areas drained by, and the connections of these veins are not well understood. For even in the work of Miller (1947), where the bronchial arteries are described in several illustrations, no specific names, other than pulmonary vessels, are given to the other vascular channels within and along the bronchial wall. It is also well known that injections of the pulmonary veins invariably fill vessels along the bronchi, and from this, it is assumed that the intrapulmonic course of the bronchial veins must drain into the pulmonary veins.

Observations made in the present study indicate that the bronchial veins are in the form of a plexus along the entire length of the bronchial tree as far distally as the respiratory bronchioles and may even anastomose with the venous capillaries around the alveoli. At various intervals this venous plexus connects by branches with the pulmonary vein; but there are also anastomoses between adjacent parts of this venous plexus by which blood could drain upward to the hilar region and into the azygos system by way of the extrapulmonic bronchial veins. Therefore, if the flow from the pulmonary veins is partly obstructed, these anastomoses along the bronchi may carry some of the blood to the azygos vein, superior vena cava, and the right atrium. This postulate was verified from observations on the lungs of cadavers in which mitral stenosis or partial occlusion of the pulmonary veins by various growths in the hilar region, resulted in enlarged bronchial veins which connected by anastomotic veins to the azygos system.

Since anastomoses do occur between the bronchial and pulmonary arteries, the plexus of vessels around the bronchi must be supplied primarily by the blood under higher pressure from the bronchial arteries, but they

could also receive additional supply from the pulmonary artery or even from the pulmonary veins. Although the latter source may seem unphysiologic, it is well known that in the beginning of inspiration, the expanding bronchi would force the blood in the bronchial veins out either into the pulmonary veins or up along the bronchial veins to the hilar region. But as the inspired air passes into the smaller bronchi and the alveoli and with full expansion of the peripheral respiratory tissue, pressure from this expanded tissue would be applied against the walls of the pulmonary veins, due to their location between the lobules and the bronchopulmonary segments, so that some of the aerated blood from the capillaries around the alveoli may be forced both along the pulmonary veins to the left atrium and some blood possibly back along the bronchial venous plexus. Although the bronchial arteries must take care of a large part of the nutritional requirements of the normal bronchial tissue, in certain diseases of the bronchi the bronchial venous plexus is greatly enlarged. This enlargement may be due to pressure from the diseased tissue on the bronchial venous plexus or its draining tributaries to the pulmonary veins, or it could be interpreted as an increased supply from the pulmonary veins carrying richly oxygenated blood to the diseased areas.

The work of Ellis and associates (1951) indicates that necrosis of the extrapulmonic course of the bronchi will occur with occlusion of the bronchial arteries, but by anastomoses of the bronchial with the pulmonary vessels, the intrapulmonic bronchi are not affected with this occlusion. Shedd and co-workers (1951) have also shown by occluding the pulmonary artery to the lungs of dogs that functional communications must exist between the bronchial and pulmonary arteries in normal lungs.

In the present restudy, as well as in reports by others, it was found that in addition to the bronchi, the bronchial arteries also supply: the midportion of the esophagus, the tracheobronchial lymph nodes, the vagus nerve in its course near and within the lungs, the vasa vasorum to the pulmonary artery, and the visceral pleura either directly or by way of anastomoses with the terminal branches of the pulmonary artery. In the last instance, Ghoreyeb and Karsner (1913), and others, have shown that certain areas of the visceral pleura may be injected by way of either the bronchial or the pulmonary arteries, depending on the pressure in the two arteries and which vessel was injected first, indicating that there must be anastomoses between the peripheral branches of the bronchial and pulmonary arteries. Other reports have also shown that bronchial vessels may also anastomose with the pericardial or cardiac vessels under certain circumstances.

COMMENT

This study suggests that the circulation to the lungs is not as simplified as some of the current concepts would indicate. Connections which may exist between the various vessels are shown in Figure 9. Among these are, normal, short or long anastomoses between the bronchial and pulmonary arteries (*6* and *7*). Shunts larger than capillaries are found between the branches of the pulmonary artery and the pulmonary veins (*3*), which may shunt blood away from a part not requiring a large circulation, or reduce the pressure to a certain area if systemic pressure from enlarged bronchial arteries or a patent ductus arteriosus conveyed blood to the area. The plexus of veins around the bronchi (*2*) drain into the pulmonary veins or, by anastomoses along the bronchus, may drain into the azygos system. The pleura may be supplied by direct branches of the bronchial arteries, particularly along the intersegmental or interlobar connective tissue septae, or by branches of the pulmonary artery which anastomose with the bronchial artery (*6*). Arteriovenous shunts may be found in the pleura (*5*).

SUMMARY

1. Studies of sectioned human embryos indicate that segmental branches of the dorsal aorta are the early blood supply to the region of the developing esophagus, trachea, and lung buds—the venous drainage from this region being into the anterior cardinal veins. Later with development of the pulmonary artery and veins, these vessels also connect

with the plexus around the region of the developing lungs, and establish anastomoses between the systemic and pulmonary circulation.

2. Injection studies of normal and pathological lungs demonstrate that anastomoses larger than capillaries exist between the bronchial and pulmonary arteries and that these anastomoses may enlarge in certain diseased conditions.

3. Shunts, larger than capillaries, were found between the pulmonary artery and veins which may be instrumental in diverting blood from enlarged bronchial (and their anastomoses with the pulmonary) arteries, or from a patent ductus arteriosus, to the pulmonary veins.

4. The bronchial veins form a plexus around the bronchi which drain into the pulmonary vein, intrapulmonically, and the azygos veins, extrapulmonically. With partial occlusion of the pulmonary veins, some of the pulmonary venous blood may flow along the bronchial veins to the azygos system, superior vena cava, and the right atrium.

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RESECTION FOR PULMONARY TUBERCULOSIS IN CHILDREN AND ADOLESCENTS

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RECENT advances in the treatment of pulmonary tuberculosis have widened considerably the scope of surgery in the management of the disease. A better selection of patients, improvements in anesthesia, as well as a more rational approach to preoperative and postoperative care have contributed their share in enlarging the field of surgery, especially resection. Of particular significance has been the widespread use of antibacterial agents which has served not only to minimize the danger of resection but has made more patients suitable for surgical treatment. One such group is children with active pulmonary tuberculosis in a stage requiring hospitalization.

Surgical treatment of pulmonary tuberculosis in children has had limited application. Extrapleural thoracoplasty has been found impractical because of the resulting scoliosis and cardiorespiratory embarrassment in the growing child. Other surgical measures such as extrapleural pneumonolyses with various fillings have been used occasionally and discarded because of their doubtful value and the risks involved. Therapeutic pneumothorax, if one might call it a "surgical" measure, has been used sporadically. Resectional surgery is practically an unexplored field. In general, the surgical treatment of pulmonary tuberculosis in children has not kept pace with the notable advances made in adults.

In 1948 when the Department of Hospitals of New York City assumed jurisdiction of Seton Hospital, the newly created staff was confronted with a group of children with pulmonary tuberculosis who were in need of active treatment in addition to the conventional measures which they had been receiving. It was decided to utilize resectional treatment. At the outset it was realized that problems might arise in the use of resectional surgery in children not met in adults. It did not take long, however, before resection was adopted as a definitive measure in selected cases.

Excisional surgery of pulmonary tuberculosis in children was begun at Seton Hospital early in 1949. At that time no study had appeared on the subject, except for isolated case reports in some of which the diagnosis of tuberculosis had not been made preoperatively. A year later Levitan and Zelman reported 4 cases of pneumonectomy for tuberculosis in children; the youngest 2½ years, the oldest 12 years. In 1951 Ross reported 7 cases of lobectomy and 6 of pneumonectomy in children aged 4 to 16 years. In the same year Batelho, Chapchap, Pereira, and Cardeiro reported 4 cases of pneumonectomy in girls 8 to 13 years of age. The several authors mentioned were favorably impressed with the results although the numbers treated were small and the follow-up period was short. In the present report are described the results of resectional surgery in a group of children and adolescents with pulmonary tuberculosis followed postoperatively for periods ranging from 6 months to 3 years, at the time of this writing.

MATERIAL

From May, 1949 to November, 1951, 30 children with pulmonary tuberculosis were presented at medical surgical conferences and passed for resection. At the time of operation, the ages of the patients ranged from 7 to 16 years. The diagnosis was verified in each instance by the isolation of acid fast organisms from the sputum, gastric, or tracheal contents. All but 1 of the 30 patients were girls. (Seton Hospital does not have the facilities for the admission of boys.) Nineteen of the patients were negroes; 7, Porto Ricans; and 4, whites.

Twenty-one of the 30 patients had been hospitalized for symptoms referable to the respiratory system; the remainder had been asymptomatic when the disease was discov-

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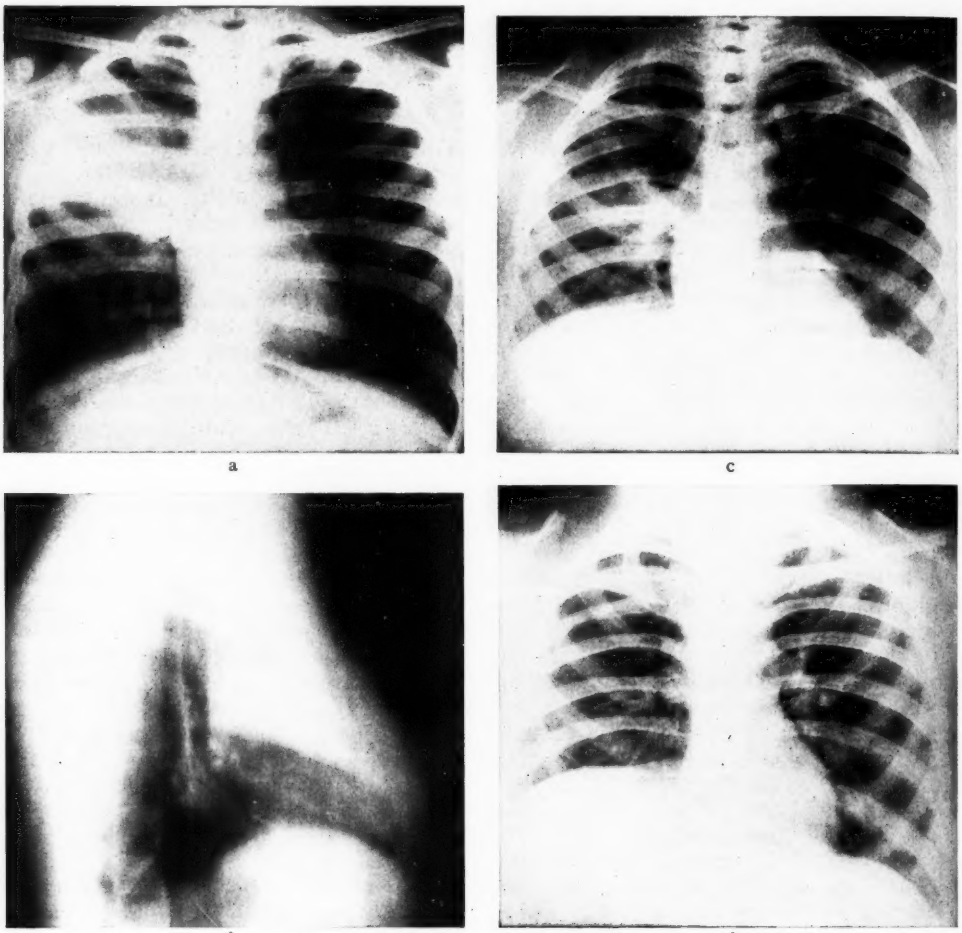

Fig. 1. (Legend on opposite page.)

ered, either during school surveys or during contact examinations. A history of tuberculosis contact was obtained in 13 cases. Two patients in the asymptomatic group developed symptoms shortly after the disease was discovered. Sixteen patients, or approximately half, had a known history of tuberculosis of from 1 to 3 years. The known duration of illness in 13 others was 6 to 12 months. One girl of 13 with advanced cavitary disease of the right middle and lower lobes was operated on 2 months after the onset of symptoms. She undoubtedly had the disease for a longer period.

On admission to the hospital, 23 of the 30 children had unilateral tuberculosis; 7 had bilateral disease. The disease in the less involved lung had cleared roentgenologically, or was considered sufficiently stabilized to permit resection of the more involved lobe or lung. Gross cavitation was demonstrable roentgenologically in 20 cases; the antra were usually small and in 4 were multiple. Large cavities were present in 3 patients with lower lobe, and

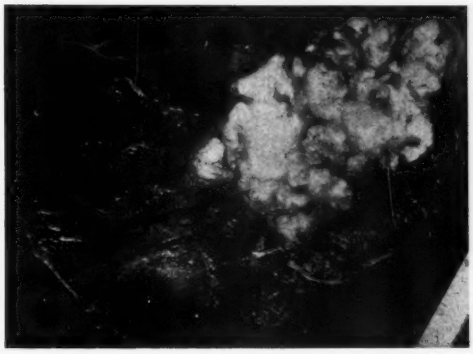

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Fig. 1. Case 1. a, Admission x-ray film, June 12, 1949, showing consolidation of major portion of right upper lobe. b, Right lateral tomogram. The disease occupies the anterior segment of the right upper lobe. c, Preoperative x-ray film, June 6, 1950. Considerable regression of disease following streptomycin treatment. d, X-ray film 21 months after right upper lobe resection. e, Section through resected right upper lobe shows the lobulated, caseous mass in anterior segment.

n 1 with upper lobe disease. Three children had round foci with central necrosis suggestive of an excavating primary complex. The remaining 10 had infiltrative disease without distinct cavitation; in 4 of these, the involved area had the appearance of segmental atelectasis.

Twenty-five of the 30 patients had bronchoscopic examinations preoperatively. In 16 no endobronchial disease was found; 4 showed mucosal edema of the bronchus of the involved lobe, and 5, narrowing of the bronchus with mucosal swelling and redness. In the presence of endobronchial disease, surgery was postponed until a later bronchoscopy revealed healing of the lesion. None of the children were found to have evidence of extrapulmonary tuberculosis at the time of operation. One child gave a history of tuberculous peritonitis which had cleared prior to admission to Seton Hospital.

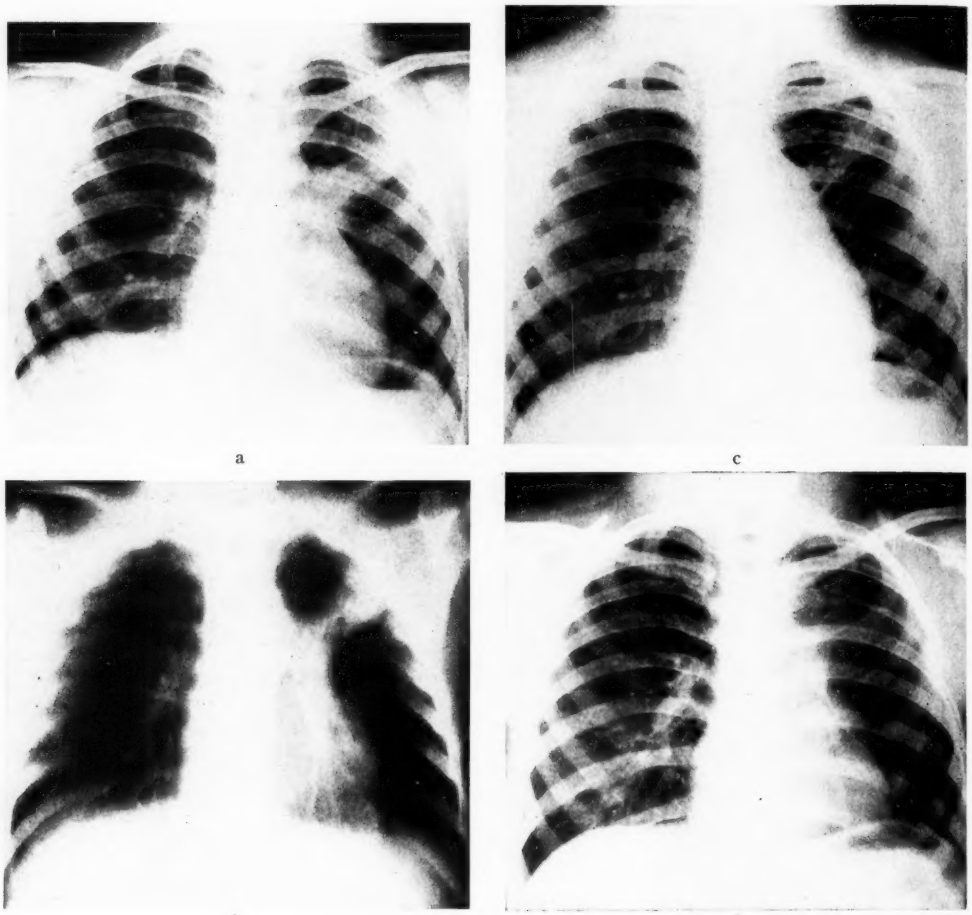
Many of the patients had received one or more courses of streptomycin and para-aminosalicylic acid before their admission. It is noteworthy that beneficial effects of the agents were often noted clinically, as well as roentgenologically, after resumption of antibacterial treatment. Unfortunately, streptomycin sensitivity tests could not be done.

TREATMENT

Pulmonary resection was the primary procedure in 21 patients. Seven children had received previously varying periods of pneumothorax treatment and 2, pneumoperitoneum. The indications for resection were based on an evaluation of the patient's course, serial x-ray films, including tomography, bronchoscopy, and, when indicated, functional studies. Surgery was done when no further regression of the disease was seen roentgenologically. At the time of operation the patients were afebrile, the weight stationary or increasing. The children were maintained on intramuscular streptomycin in the preoperative and postoperative periods. In the presence of endobronchial disease, aerosol penicillin and streptomycin were also given.

An appraisal of the amount of lung requiring resection was made on the basis of the chest x-ray films, including tomograms in the anteroposterior and lateral projections. A close correlation was found between the preoperative estimate of the amount of lung grossly involved and that resected. However, in 3 cases shrunken segments were found adjacent to the mediastinum whose presence had escaped detection prior to operation. These involved the medial segment of the middle lobe in one, the medial segment of a lower lobe in another, and the inferior segment of the lingula in a third. Every effort was made to conserve lung tissue and to avoid pneumonectomy. On the other hand, no lobe or segment with significant disease was spared.

Of the 30 children who came to operation, resection was done in 27. In 3 cases resection was not performed. A girl of 7 died of cardiac arrest when the hilar dissection for a contemplated left pneumonectomy was begun. In a second case the presence of disease in



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the right upper lobe precluded a planned right lower lobe lobectomy. Pneumonectomy was not done because of recently stabilized disease in the contralateral lung. The patient has since received pneumoperitoneum with some improvement. In the third case, a 13 year old boy was scheduled for resection of the apicoposterior segment of the left upper lobe. Following extrapleural mobilization of the lobe, it was noted that a thickened pleura accounted for the roentgenologic changes. The operation was therefore not completed. The patient has been doing satisfactorily since. One patient had bilateral lobectomy, the left lower lobe being removed at one operation and the right upper lobe 15 months later. This case accounts for the additional operation noted in Table I.

Anesthesia was induced with nitrous oxide and oxygen or pentothal sodium and then carried through the operation with endotracheal ether or cyclopropane or both. The patients were operated on in the lateral recumbent position through a posterolateral incision. Individual ligation of the hilar structures was performed in every instance. The bronchus was closed with a single row of No. 0000 inter-

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Fig. 2. Case 2. a, Admission x-ray film, June 18, 1951, showing density in left upper lobe. b, Anteroposterior tomogram showing posterior location of disease. c, Preoperative x-ray film, October 5, 1951. Regression of lesion following streptomycin treatment. d, X-ray film 6 months after left upper lobectomy. e, Section through left upper lobe showing irregular area of caseation.

rupted silk sutures and covered with pleura. Phrenic nerve crush was done in 2 cases. Thoracoplasty was required in 2 patients, in both following a right-sided pneumonectomy. In a 15 year old asthmatic girl, thoracoplasty was done 6 months after pneumonectomy to reduce undue mediastinal shift. However, little change in the position of the mediastinum was obtained. A right thoracoplasty was done in another 15 year old girl because of a feeling of tightness in the chest and palpitation. The symptoms abated following the operation. No significant scoliosis occurred in either case, 2 and 1 years respectively since the operation. Thoracoplasty was not found necessary in 2 patients who had a left pneumonectomy; neither was it done in any patient with lobectomy or segmental resection.

Operative deaths. There were 2 operative deaths. A 7 year old girl for whom a left pneumonectomy was contemplated died of cardiac arrest after the pleural cavity was entered and the hilar dissection begun. The patient did not respond to cardiac massage, artificial respiration, and intracardiac injections of adrenalin and procaine. The second death occurred in a 13 year old girl 8 hours after a right pneumonectomy as a result of respiratory insufficiency. She had been ill for 2 years with bilateral pulmonary tuberculosis. The left lung was considered roentgenologically free of disease at the time of operation. There had been no clinical evidence of impaired pulmonary function but, unfortunately, bronchospirometric studies were not available at that time. At autopsy, diffuse interstitial changes were found in the remaining lung probably accounting for the fatality.

Postoperative complications. There were few complications encountered. The most serious problem was the retention of bronchial secretions because of the patients' fear of deep breathing and coughing. Tracheal aspirations usually sufficed in cleansing the passages. Three children who had lobectomy developed atelectasis of the remaining lobe which promptly re-expanded following bronchoscopy

TABLE I.—OPERATIVE PROCEDURES IN 30 PATIENTS

	No. of cases	No. of operations
Segmental resections		4
Apicoposterior, left upper lobe	2	
Apicoposterior and anterior, left upper lobe	1	
Lateral, right middle lobe	1	
Lobectomies		19
Unilateral		
Right upper lobe	6	
Right upper and middle lobes	1	
Right middle and lower lobes	1	
Right lower lobe	3	
Left upper lobe	5	
Left upper lobe and superior segment left lower	1	
Bilateral		
Left lower lobe and right upper lobe	1*	
Pneumonectomies		5
Right lung	4	
Left lung	1	
Thoracotomy: no resection		3

*Right upper lobe removed 15 months after left lower lobe.

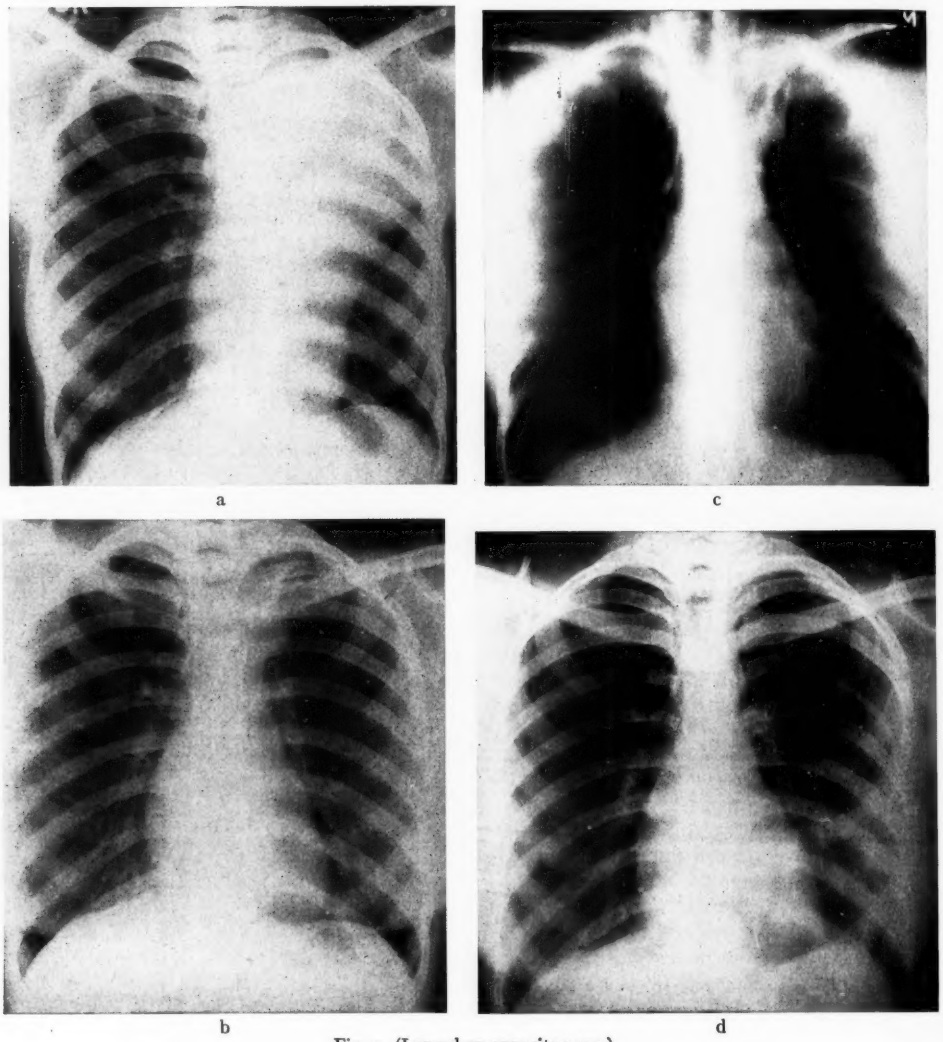

Fig. 3. (Legend on opposite page.)

and aspiration of secretions. In recent cases, efocaine injected into the intercostal nerves at operation has been helpful in reducing postoperative pain. There was not a single instance of wound infection, empyema, or bronchopleural fistula. In 1 case postoperative spread occurred to the right upper lobe following a left lower lobe lobectomy. Fifteen months later a right upper lobe lobectomy was done. The postoperative course was uneventful and the patient was discharged. She was readmitted to the hospital 3 months later with reactivation of tuberculosis in the lingula which had been found slightly diseased at operation. She is improving under isonicotinic hydrazide treatment.

Pathologic findings. In 20 cases the involved lung contained nodular caseous foci varying in

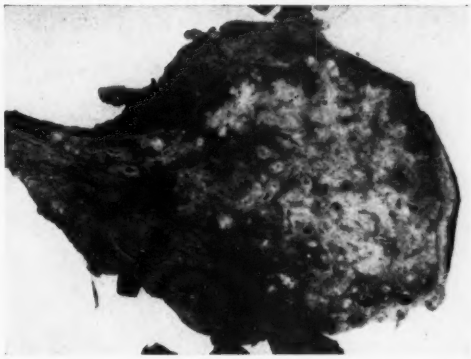

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Fig. 3. Case 3. a, Admission x-ray film, May 5, 1950, showing extensive disease of the left upper lobe. b, Preoperative x-ray film, December 8, 1950, showing marked resolution following streptomycin treatment. c, Preoperative tomogram showing disease limited to apicoposterior segment of left upper lobe with small cavity. d, Postoperative x-ray film, July 9, 1951. e, Section through apicoposterior segment of left upper lobe.

size from a few millimeters to 3 centimeters in diameter. The consistency of the affected tissue depended on the number and coalescence of these foci. In 6 cases circumscribed disease was found and in 2, segmental atelectasis. In , the entire lung was found markedly contracted and fibrotic. Of 23 patients submitted to lobectomy, 9 showed small foci in the remaining lobe, usually situated subpleurally. These were not considered sufficiently extensive to warrant additional sacrifice of lung tissue. Surprisingly enough, enlarged tracheobronchial lymph nodes were encountered in only 4 patients. Lymph node involvement was greatest in the pneumonectomy cases. Considerable fibrosis was often found at the hilum, especially in the younger children, necessitating careful dissection of the region to avoid hemorrhage.

Microscopy revealed the diseased areas to consist of caseation with little or no fibrotic reaction or encapsulation. Cavities were found in 15 specimens. These were usually small but in 5 were multiple. In 5 patients whose roentgenograms of the chest had shown cavitation, the specimens revealed solid caseous foci. Large cavities were encountered in 3 cases, all in the lower lobes. The walls of the cavities consisted of caseous tissue which merged with the surrounding lung and did not show much fibrotic reaction. The large bronchi showed little involvement but there was extensive tuberculosis of the smaller bronchi in many cases. This is a striking feature of tuberculosis in children. The generally accepted indices of stabilized disease in children are not borne out by the pathological findings. A detailed report of the pathology of the resected specimens will be published by Dr. Ruth Lubliner, pathologist at Seton Hospital.

ILLUSTRATIVE CASE REPORTS

CASE 1. C. G., a 9 year old negro girl became ill in April, 1949 with fever and chest pain. On admission to Seton Hospital, May 12, 1949, x-ray films of the chest revealed an area of consolidation confined to the anterior segment of the right upper lobe (Fig. 1a, b). Gastric cultures were positive for acid fast organisms. Bronchoscopy revealed compression of the right upper lobe bronchus. On bed rest and streptomycin considerable diminution occurred in the size of the infiltration (Fig. 1c). On June 7, 1950, a right upper lobe lobectomy was done. The postoperative course was uneventful. The patient has been followed in the clinic for 2 years and has continued to do satisfactorily (Fig. 1d).

The resected specimen, contained a large, lobulated, encapsulated mass compressing the adjacent bronchi (Fig. 1e). On microscopic examination the lesion consisted of central caseation surrounded by a broad zone of tuberculous granulation tissue which in turn was walled off by fibrous tissue. This tuberculoma-like lesion did not involve the adjacent bronchi.

CASE 2. G. D., an 11 year old Porto Rican girl developed a cough in April, 1951. Her stepfather was known to have pulmonary tuberculosis. The admission chest x-ray film on June 18, 1951 showed an area of consolidation in the left upper lobe (Fig. 2a and b). The sputum was positive for acid fast bacilli. The patient was treated with bed rest and streptomycin with some degree of resolution of the lesion (Fig. 2c). On October 19, 1951, a left upper lobe lobectomy was done. The postoperative course was uneventful. The patient is well and attending the surgical clinic (Fig. 2d).

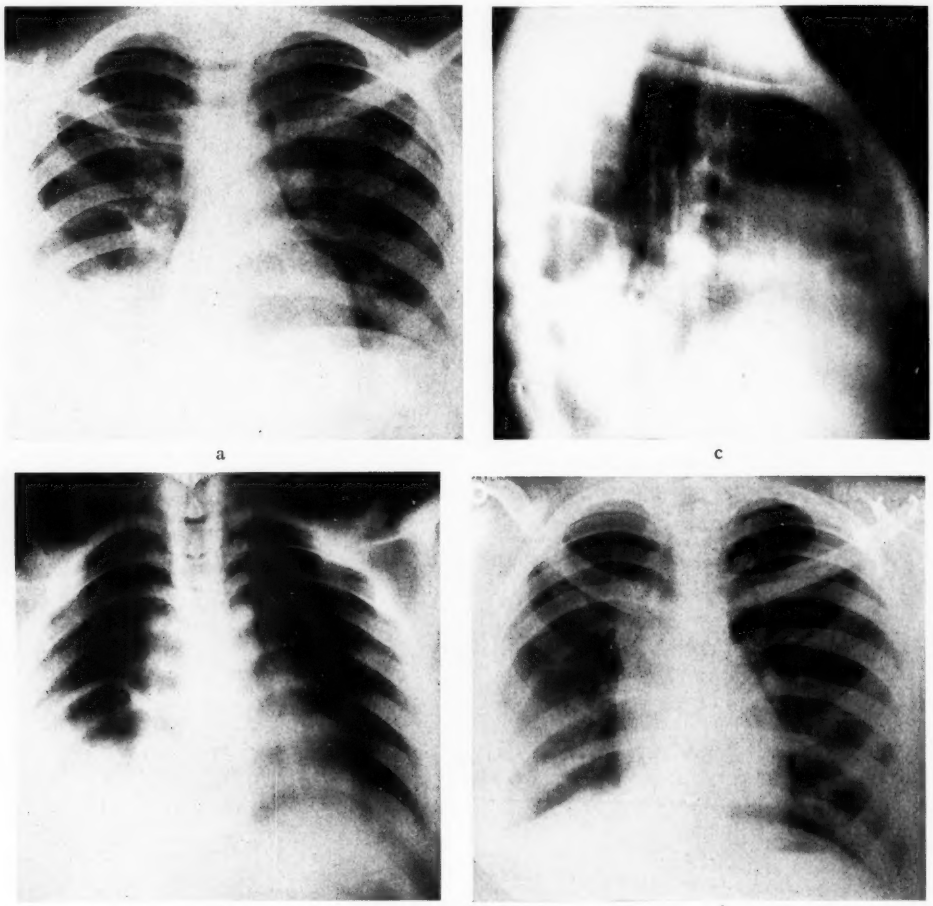

Fig. 4. (Legend on opposite page.)

The resected lobe revealed in the posterior segment an irregular area of caseation with central cavitation (Fig. 2e). There were also scattered caseous foci, many involving small bronchi. Microscopically, the lesion consisted of large caseous foci separated from the surrounding lung tissue by broad zones of tuberculous granulation and dense fibrous tissue. The hilar nodes contained small discrete tubercles. The bronchi revealed mucosal and submucosal tuberculous infiltrations.

CASE 3. R. W., a negro female, became ill in December, 1949 at the age of 15 with cough, chest pain, and fever. She was a known luetic, having received penicillin therapy. The admission chest x-ray film in May, 1950 (Fig. 3a) revealed extensive tuberculosis of the left upper lobe. The sputum was positive for acid fast bacilli. She was treated with bed rest and streptomycin with considerable resolution of the lesion (Fig. 3b and c). Bronchoscopy was negative. On December 11, 1950 a resection of the apicoposterior segment of the left upper lobe was done. She made an uneventful recovery, and has been followed in the clinic for the past 18 months (Fig. 3d).

The resected segment (Fig. 3e) contained numerous caseous foci and an irregular cavity with caseous walls. Many of the caseous foci surrounded small bronchi; others were spread throughout the parenchyma.

CASE 4. E. M. M., a 13 year old negro female became ill in September, 1950 with fever and chest pain. She was admitted to Seton Hospital on October 26,

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Fig. 4. Case 4. a, Admission x-ray film, November 3, 1950, showing a large cavity in right lower lobe. b, Anteroposterior tomogram. c, Right lateral tomogram showing shrunken right lower lobe with large cavity and disease in the middle lobe. d, X-ray film 19 months after right lower and middle lobe resection. e, Cross-section of resected right middle and lower lobes showing collapsed cavity and caseous foci.

1950 where tuberculosis of the right middle and lower lobes was found (Fig. 4a, b, and c). A large cavity was present in the shrunken right lower lobe. Following a short course of streptomycin therapy a right middle and lower lobe resection was done on November 30, 1950. On the second postoperative day bronchoscopic aspiration was done for retained secretions. She has been followed in the surgical clinic for a period of 18 months and is doing well (Fig. 4d).

The resected lobes were completely consolidated with coalescing caseous foci ranging from 0.5 to 2 centimeters in diameter (Fig. 4e). The lower lobe contained a cavity, the walls of which consisted of caseous material. Many of the caseous foci were located at the site of completely destroyed bronchi which were recognizable by bits of mucosa or cartilage.

CASE 5. M. B., a 13 year old negro girl was found to have pulmonary tuberculosis on routine x-ray examination of the chest. Her mother and uncle had tuberculosis. She was symptomatic at the time the disease was discovered. She was admitted to Seton Hospital on April 14, 1951. X-ray examination of the chest revealed extensive involvement of the entire left lung (Fig. 5a and b). The sputum contained acid fast bacilli. In view of the extent of involvement and good condition of the patient, she was prepared for surgery with streptomycin and para-aminosalicylic acid. On June 20, 1951 a left pneumonectomy was done. The postoperative course was uneventful. She has been followed in the surgical clinic for a year and has continued to do well (Fig. 5c).

The left lung consisted of a markedly shrunken and consolidated upper lobe which contained confluent caseous areas. A similar but less extensive involvement was noted in the lower lobe (Fig. 5d). Microscopic examination revealed extensive caseous tuberculosis; many of the small bronchi were destroyed and the walls replaced by tuberculous granulation tissue.

RESULTS

Table II shows the status of 28 patients who had resectional treatment. The patients have been followed for periods ranging from 6 to 36 months; in 13, for a year or longer. All but 1 of the patients discharged attend the Seton Out Patient Department, 1 has returned to Porto Rico and is being followed by letter.

Twenty-five of the 26 children are well, in good nutrition and without symptoms. Repeated roentgenograms of the chest show no evidence of active tuberculosis; the sputum or gastric contents remain free of acid fast organisms. The patient referred to previously who had bilateral lobectomy is in the hospital with active disease in the lingula of the left upper lobe. Another girl, now 15 years of age, had a left upper lobe lobectomy and resection of the superior segment of the lower lobe. At operation a nodule was felt deep in the remaining basal segment which was not removed.

TABLE II.—PRESENT STATUS OF 30 PATIENTS 6 MONTHS TO 3 YEARS LATER

		No. of cases
Resected cases		28
Living and well	25	
Living with active tuberculosis	1	
Dead	2	
Operative	2	
Late	0	
Nonresected cases		2
Living and well	1	
Living with active tuberculosis	1	
Total		30

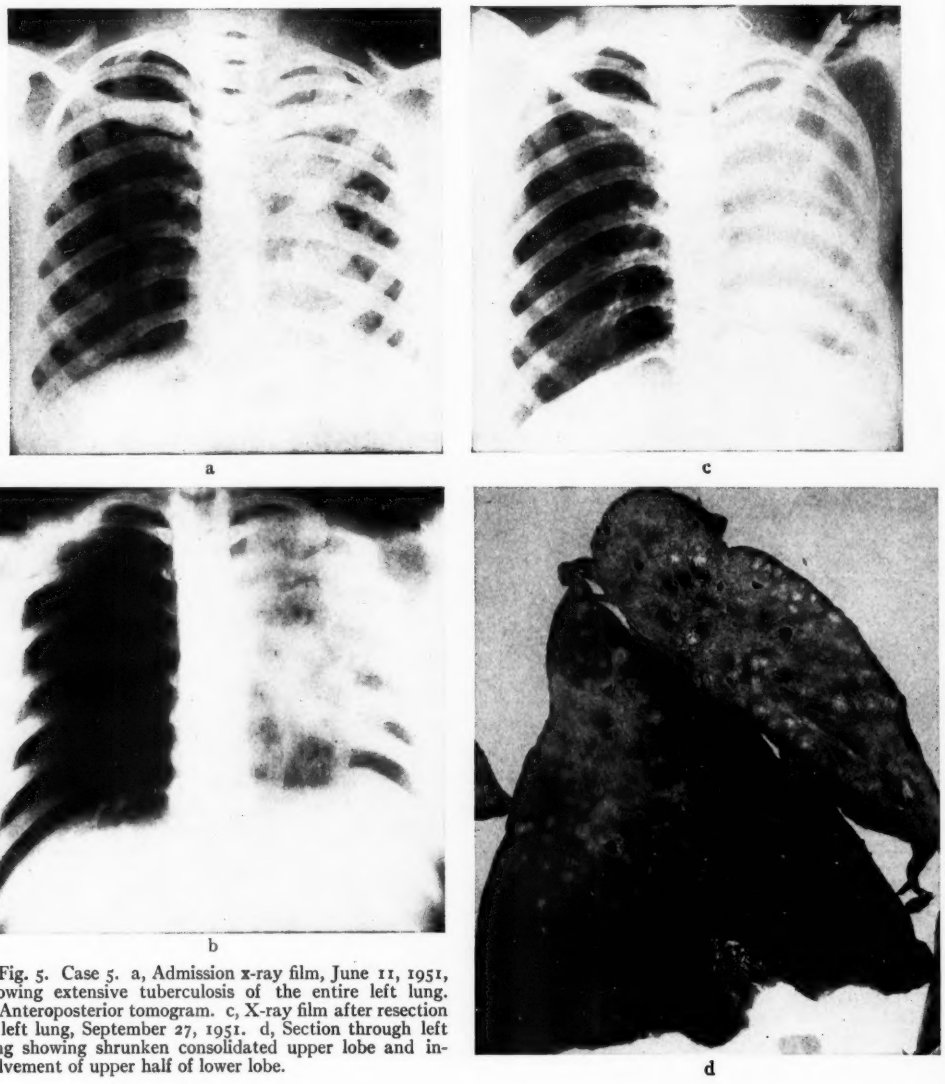

Fig. 5. Case 5. a, Admission x-ray film, June 11, 1951, showing extensive tuberculosis of the entire left lung. b, Anteroposterior tomogram. c, X-ray film after resection of left lung, September 27, 1951. d, Section through left lung showing shrunken consolidated upper lobe and involvement of upper half of lower lobe.

Twenty-two months later roentgenograms of the chest revealed an increase in the size of this focus and the sputum became positive. The patient was readmitted to the hospital and given another course of antibiotics and bed rest. The lesion regressed and the patient was discharged to the clinic.

SUMMARY

Children with active pulmonary tuberculosis may be treated with resection in the same manner as adults. The patients stand major surgery well and make rapid recovery. The resiliency of lung tissue in children reduces the tendency toward overdistention of

the remaining lobes, a problem encountered in adults. The nature of the pathologic changes associated with tuberculosis in children make resectional surgery the treatment of choice when other indications are in keeping.

Our initial fears that resectional treatment in children might be handicapped by the type of disease was found groundless. By the time a tuberculous process in the lung of a child reaches a stage requiring surgery, it is academic whether it be primary or postprimary. The principles underlying treatment of a disease which has progressed to irreparable destruction of lung tissue are basically the same. Since the ultimate results of any form of treatment of tuberculosis depend primarily on the course of the disease, as determined by natural processes of healing, one cannot prognosticate the final outcome.

CONCLUSIONS

1. Thirty (30) children and adolescents with pulmonary tuberculosis were treated with excisional therapy. At the time of operation they ranged between 7 and 16 years of age. All but 1 of the patients were females.

2. Pulmonary resection was completed in 27 cases. The findings at operation precluded a contemplated resection in 2. There were 2 deaths in the group. One patient died of cardiac arrest during the operation; the other, died 8 hours after a right pneumonectomy as a result of respiratory failure. There were no late deaths.

3. The retention of secretions due to fear of coughing was the only major problem encountered postoperatively. There was 1 postoperative spread.

4. The 26 patients who successfully underwent resection have been followed from 6 months to 3 years. Twenty-five are well. One patient had reactivation of a pre-existing disease in the left upper lobe 18 months following a left lower lobe lobectomy and right upper lobe lobectomy.

5. Resection has a definite place in the treatment of pulmonary tuberculosis in children.

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HEART-LUNG BY-PASS USING PUMPS AND ISOLATED HOMOLOGOUS LUNGS

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THE present communication deals with observations obtained in experimental by-pass of blood around the heart and lungs in dogs. The method involves the use of two simple extracorporeal pumps previously described (20–22) in series with an extirpated set of another dog's lungs for purposes of extracorporeal oxygenation. Also, pilot studies on the use of heterologous lungs will be discussed.

At the present time the perfection of by-pass procedures to create an essentially bloodless heart is being investigated along three main avenues of approach. The most direct approach involves by-pass of the heart alone, using the animal's own lungs as the means of oxygenation of blood. This approach is considered to be fundamental inasmuch as it is today a practical laboratory method of studying basic cardiac and circulatory physiology, a thorough knowledge of which must be attained before routine by-pass procedures can be applied to successful human intracardiac surgery. The accumulation of evidence demonstrates that by-pass of the heart using pumps alone is compatible with the maintenance of normal physiologic responses of the rest of the organism including the lungs, brain, and kidneys. Sewell and Glenn reported successful by-pass around the right heart with recovery of dogs. Other workers, including Kantrowitz, Sirak, and Clowes by-passed the left heart in experimental animals that recovered. The authors (20–22) previously reported their observations using simple pumps to by-pass the right and left sides of the heart individually and simultaneously with recovery and prolonged survival of dogs.

Simple cardiac by-pass will probably have limited application to the human subject even though its effectiveness in the laboratory is well established. Since thoracotomy is necessitated by this approach, its use as an aid to the failing heart is not practical. Simple by-pass may be useful in intracardiac surgery which in itself requires thoracotomy. Human application, using only simple pumps, will probably be limited to one-sided procedures involving by-pass of one side of the heart. Procedures have been developed to by-pass either side of the heart alone with essentially bloodless atrium and ventricle on the by-passed side. Bilateral intracardiac procedures would necessitate the use of two pumps with four cannulations. Although all four cannulations may be accomplished via a one-sided (left) thoracotomy, the cannulation procedure is complicated compared to other approaches. The attainment of "dry" atria would involve relatively complicated maneuvers and perhaps bilateral thoracotomy.

The second approach, established by Gibbon, involves by-pass around the heart and lungs using pumps and some type of mechanical oxygenator. Notable contributions to this most complicated problem have been made by Gibbon and associates, Dennis and associates, Jongbloed, and Björk. The eventual apparatus for routine intracardiac surgery will probably be of this type; i.e., a pump-oxygenator, although further development of mechanical oxygenators is necessary. Recent progress in this approach suggests that such development is imminent.

The third approach to the production of a bloodless heart involves by-pass of the heart and lungs using simple pumps to assume the function of the heart while extra-

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corporeal oxygenation is accomplished using extirpated homologous lungs. The literature has a few scattered reports of the use of isolated lungs for oxygenation of blood. The heart-lung preparation was first described by Martin at Johns Hopkins in 1881 and later more thoroughly investigated by Starling. The preparation utilized isolated lungs, artificially respired, to provide oxygenated blood for the working heart. Among the early investigators of organ perfusion, Jacobj working at Strasbourg constructed an elaborate mechanical pump and in 1895 reported the use of isolated autologous lungs for aeration of perfusate. Embly and Martin (1905), employing a similar arrangement, aerated the autologous lungs with a mixture containing chloroform to study the latter's action on isolated intestine and kidney. Hemingway (1931) also perfused kidneys using autologous lungs for aeration. Dale and Schuster, who in 1928 first reported the air-piston pump which has become the basis for many of the present-day heart pumps, used isolated lungs from the same animal in the perfusion of hind-quarters of cats and dogs. Barcroft (1933) seems to have been the first to report maintenance of the circulation of an entire animal using a mechanical heart and isolated homologous lungs. He used a heart-lung preparation to aerate the blood and an "Albany" rotary pump to perfuse 2 dogs weighing 10 kilograms each; he reported no survival experiments. A report of our preliminary observations using homologous donor lungs has been published (19). Recently both Mustard and Potts have reported their preliminary results of the use of isolated homologous lungs and mechanical pumps during heart-lung by-pass.

METHOD

Preparation of the pumps. On the morning of the experiment, healthy mongrel dogs were given 2 milligrams of heparin per pound of body weight by the intravenous route and subsequently exsanguinated. The blood was collected in sterile bottles and was used to prime the pumps as well as to transfuse the experimental animal during operation. No added heparin was administered to the experimental animal. The pumps, previously described in detail (22), had been filled with a 1:1,000 solution of zephiran hydrochloride 18 hours prior to use. The input and output leads and cannulas had also been cold sterilized in zephiran. The pumps were then rinsed twice with sterile saline and primed with blood, care having been taken to minimize trauma to the blood. During priming, the output lead of each pump was connected to the respective input lead; after priming, the leads were individually clamped and disconnected one from the other. The pumps at this point were ready for connection to the appropriate cannulas.

Collection of donor lungs. One of the unanesthetized animals exsanguinated for blood donation was selected. The chest was entered under aseptic conditions by excision of the sternum and costal cartilages. The following structures were serially divided between ligatures: the azygos vein, the superior and inferior venae cavae, the brachiocephalic and left brachial arteries, and the descending aorta. The diaphragmatic attachments of the pericardium and the pulmonary ligaments were divided, and the heart, lungs, and trachea dissected free from the esophagus. The trachea was transected at the level of the first rib and the entire specimen of cardiorespiratory circuit was removed from the chest. The heart was removed with the donor lungs because it supplied convenient cannulation sites. The specimen was placed into a basin and the trachea ligated to the inner end of a spout piercing the wall of the basin. The outer end of the spout was fitted with a rubber adapter. The lungs were at this point reinflated by mouth insufflation and maintained in an inflated position by clamping the rubber adapter. A glass cannula was placed through the wall of the right ventricle into the main pulmonary artery and held fast by means of a ligature about the wall of the artery. A glass cannula was then placed into the left atrium via an incision through the wall of the appendage; it was held in place by means of a ligature about the appendage. The outside

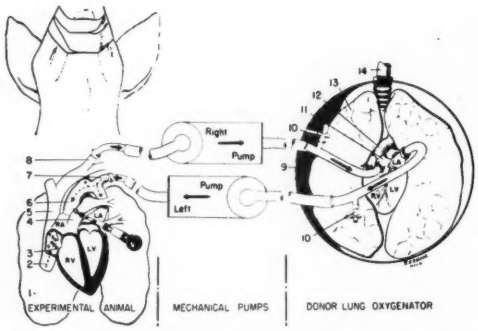


Fig. 1. Schematic diagram of blood circuit during heart-lung by-pass. Arrows depict the direction of blood flow. *1*, Collapsed lungs of the experimental animal; *2*, inferior vena cava; *3*, opening of coronary sinus; *4*, main pulmonary artery; *5*, superior vena cava; *6*, aorta; *7*, left brachial artery containing cannula delivering oxygenated blood to the systemic circuit of the experimental animal; *8*, left external jugular vein through which the right atrial cannula is inserted to deliver unoxygenated blood from the experimental animal into the right pump (Note the Blalock clamp occluding the main pulmonary artery); *9*, donor lung basin; *10*, side-arms on donor-lung cannulas; *11*, main pulmonary artery containing cannula delivering blood tor oxygenation by the donor lungs; *12*, aorta of donor heart-lung preparation (ligated distally); *13*, homologous donor lung; *14*, rubber adapter on outside of spout piercing donor lung basin.

diameter of both glass cannulas was 13 millimeters. A layer of saline solution was placed into the basin which was then covered with a lucite cover. A hole in the cover allowed the cannulas to project through. The homologous donor lungs were ready for use at this point.

Cannulation of the experimental animal. Healthy mongrel dogs, weighing 27 to 41 pounds, were anesthetized using intravenous pentobarbital sodium. The left chest and neck were shaved as were the four legs and right groin. The right femoral vessels were cannulated with polyethylene catheters. The arterial catheter was connected to a mercury manometer to record arterial blood pressure during the procedure. The femoral vein catheter was connected to a continuous intravenous drip of 5 per cent dextrose. Venous and arterial blood samples for tests were drawn through these catheters at certain points during the procedure. The left chest and neck were then prepared and draped using aseptic precautions. A small incision along the superior border of the left superficial pectoral muscle was made, and the external jugular vein dissected free, preparatory to cannulation. The left chest was entered via an incision through the bed of the resected left fourth rib. Artificial respiration was maintained by means of a modified Air Corps respirator via an endotracheal tube using oxygen. The left brachial artery was dissected free, doubly ligated at its site of branching, and occluded at its origin with a serrefine clamp. It was transected as high as possible. A glass cannula was placed into its proximal stump as the cut end was triangulated with stay sutures. The cannula was ligated into place. Ten per cent procaine was instilled into the pericardial sac and the pericardium incised. A loosely placed umbilical tape was placed about the main pulmonary artery. A polyethylene catheter with a multiperforated tip was then inserted through an incision in the left external jugular vein and threaded inferiorly until its tip lay within the right atrium. At this point all preparations were completed for the institution of heart-lung by-pass.

Institution of heart-lung by-pass. The right pump input lead was connected to the right atrial cannula in the experimental animal. The right pump output lead was attached to the cannula in the main pulmonary artery of the donor lung preparation. The left atrial cannula of the donor lung was connected to the input lead of the left pump. Air was withdrawn from both donor lung cannulas through side-arms. The left brachial artery cannula was filled with blood by momentary opening of the serrefine clamp on the artery. This clamp was removed after the cannula was connected to the output lead of the left pump. The circuit of blood flow was as follows: right atrium to right pump to donor lungs to left pump to left brachial artery (see Fig. 1).

Both pumps were begun at a rate of 150 strokes per minute and the clamps were simultaneously removed from all four pump leads. The stroke of each pump was slowly increased until the slightest drop in each reservoir level was noted. A constant vacuum of minus 40 millimeters of mercury was

then applied to each reservoir. The stroke of each pump was then adjusted to maintain a constant reservoir level in each pump. Blood was added directly into the left pump reservoir from an overhead tank for transfusions as needed. When the pumps were begun, the artificial respirator was disconnected from the endotracheal tube in the experimental animal and attached to the outer end of the spout on the donor lung basin. Adequate ventilation of the donor lungs and good color of the left pump blood was obtained using endotracheal pressures of 10 to 12 centimeters of water. At this point, the heart and lungs of the experimental animal were completely by-passed with the exception of the bronchial circulation return to the left atrium, which was negligible for our purposes. The main pulmonary artery of the experimental animal was occluded to ensure complete by-pass. The heart was noted to collapse although it maintained a beat of a relatively small amplitude. The perfusion of the animal was carried on for 2 hours. Electrocardiographic and electromanometric tracings and blood samples were obtained at various times during the entire procedure.

Removal of cannulas and repair of incisions. At the end of 2 hours of pump activity, the occlusion was released from the main pulmonary artery and the input and output leads of both pumps clamped. The result was sudden cessation of heart-lung by-pass. The heart immediately resumed its circulatory function. The artificial respirator was then disconnected from the spout of the donor-lung basin and attached to the endotracheal tube in the experimental animal. The lungs were easily reinflated. Rhythmical inflation of the lungs was maintained by the artificial respirator at endotracheal pressures of 10 to 15 centimeters of water. The right atrial cannula was then removed and the left external jugular vein ligated. The left brachial artery was doubly ligated at its origin and the cannula removed. Protamine sulfate was administered intravenously until the clotting time returned to less than 12 minutes by the three tube test. The amount of protamine necessary varied from

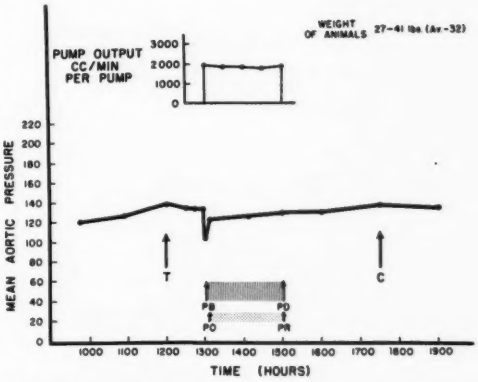


Fig. 2. Graph of mean aortic blood pressure. (Average values of 5 consecutive experiments.) *T* = time of thoracotomy, *C* = time of chest closure, *PB* and *PD* = times of pump beginning and discontinuation respectively, *PO* and *PR* = times of occlusion and release, respectively, of the main pulmonary artery. Note that the normal mean aortic pressure in dogs averages 120 millimeters of mercury.

50 to 100 milligrams. The brachial artery bed was repleuralized. The pericardium was left open. Hemostasis was then checked and all bleeding points were secured by silk ligature. The chest and neck wounds were then carefully closed in layers with silk. The animal was observed for a period of 1 to 2 hours after chest closure. The blood pressure remained stable. Thoracentesis was done to remove air and blood; aqueous penicillin and streptomycin were instilled into the pleural cavity. The cannulas were removed from the femoral vessels which were simply ligated. The femoral incision was closed with silk and the dog put in his cage.

Postoperative care. The animals were observed daily for the first postoperative week, and weekly thereafter until death or sacrifice. Each dog was evaluated clinically as regards general behavior and activity, occurrence of possible central nervous system complications, the local conditions in the chest and the diet tolerated. Certain tests were done at intervals; these included electrocardiographic tracings, hematocrit and plasma hemoglobin determinations and others. The animals were given intramuscular depot penicillin every other day during the first postoperative week.

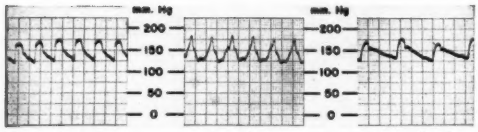


Fig. 3. Electromanometric tracings taken from within the abdominal aorta. The two end pulse wave forms are due to ventricular ejection while the middle tracing is due to pump activity; all tracings compare favorably as regards systolic, diastolic, and pulse pressures. Note the linear rise and fall of the pulse waves due to pump activity.

OBSERVATIONS

Artificial maintenance of the circulation. During the period of by-pass around the heart and lungs, the circulation is adequately maintained by the extracorporeal pumps. At the time of initiation of heart-lung by-pass there is a transient drop in the arterial tension that is not seen at initiation of heart by-pass using the animal's own lungs. This transient drop is probably due to temporary reduction in the circulating blood volume, the result of filling the pulmonary vascular tree of the exsanguinated donor lungs. This drop in blood pressure is immediately rectified by transfusion of 100 cubic centimeters of blood. The drop is not seen if 100 cubic centimeters of blood are transfused at the time of initiation of heart-lung by-pass. Figure 2 is a graph of mean aortic blood pressure plotted from the average values of 5 consecutive experiments in which heart-lung by-pass was carried on for 2 hours. The average weight of these 5 animals was 32 pounds; the average amount of infused blood during the 10 hour period of the procedure was 670 cubic centimeters. This amount is considered to be equal to the total loss of blood during the procedure; i.e., operative loss plus loss into the donor lungs.

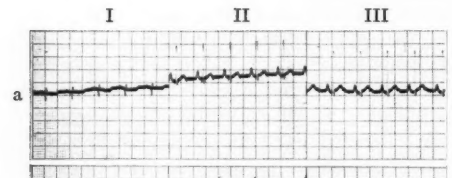


Fig. 4. Electrocardiographic tracings. I, II, and III refer to the standard limb leads. Tracings a were taken prior to thoracotomy; tracings b were taken at the end of 2 hours of heart-lung by-pass; and tracings c were taken on the first postoperative day. Note the relatively minor changes during heart-lung by-pass.

The completeness of the by-pass was demonstrated by (1) maintenance of normal arterial tension and absence of dilatation of the right heart during complete occlusion of the main pulmonary artery, (2) maintenance of 100 per cent arterial oxygen saturation during collapse of both lungs of the experimental animal, and (3) absence of pulse wave forms due to ventricular ejection on electromanometric pulse wave tracings taken from within the abdominal aorta. In Figure 3 the differences between the pulse wave forms, due to left ventricular ejection, and to pump activity can be seen. The bronchial circulation return to the left atrium is the only possible source of heart blood not diverted into the extracorporeal lung-pump system. Since the collapsed heart continues to beat during the by-pass, it is presumed that this scanty return to the left heart is pumped into the aorta by the left ventricle. The amount of this venous return to the left atrium in the experimental dog is not sufficient detectably to decrease the oxygen saturation of the aortic blood.

Electrocardiographic tracings show very little change during heart-lung by-pass. Such changes as occur (Fig. 4) are probably on the basis of axis changes and revert to normal very early in the postoperative period.

Body temperature. The extracorporeal pump-oxygenating system is not heated and, therefore, a cooling effect on the blood was anticipated. In order to determine the effect of blood cooling on body temperature, repeated determinations of the rectal temperature were done during 2 experiments. The basal control

temperatures were between 100 and 101 degrees F. The minimum temperature of about 90 degrees F. occurred at 75 minutes of by-pass; the rectal temperature remained about the same until 120 minutes of by-pass at which point the by-pass was discontinued. Following this, the rectal temperature gradually rose until, 4 hours after the chest was closed, the rectal temperature was again normal. The animals appeared to suffer no adverse effect from the temporary 10 degree drop in body temperature. This degree of temperature reduction is equivalent to that observed by us during simultaneous by-pass of both sides of the heart using the animal's own lungs as the means of oxygenation of blood.

Function of the homologous donor lungs. The isolated donor lungs serve as an efficient oxygenator and remover of carbon dioxide. It seems likely that they also aid in the removal of incidental bacterial contaminants. Whether these lungs serve other functions is not known. In preliminary experiments previously reported (19), the isolated lungs showed a marked tendency to the occurrence of edema at the time of initiation of the by-pass. In the present series of experiments edema has not been a major problem. Certain details are considered important in the prevention of this complication; these are: heparinization of the donor animal prior to removal of the lungs; complete exsanguination of the donor animal; immediate reinflation upon removal of the donor lungs and maintenance of the inflation until use; the elimination of air in the blood circuit; avoidance of torsion of the lung hila; and the use of low endotracheal pressures (10 to 12 centimeters of water) in the respirator during by-pass. Physiologic saline has been found to be an adequate moistening agent. The allowable lapse of time between sacrifice of the donor animal and use in the by-pass circuit is not definitely known. In our experience a lapse of 5 hours has resulted in no impairment of oxygenation or serious edema. Potts and associates recently reported failure of canine homologous donor lungs refrigerated overnight. Further studies of the allowable time factor are being done by us at present. It is not known how long fresh donor lungs can be perfused with good function. We have continued by-pass procedures for as long as 3 hours with good function and without noteworthy edema of the donor lungs. During a few subsequent experiments it was found necessary to increase the endotracheal pressures to 30 centimeters of water to maintain proper oxygenation. In these cases it was noted that the lower lobes of the donor lungs were edematous and that simple ligation at the hila of these edematous lower lobes allowed excellent oxygenation at normal (10 to 15 centimeters of water) endotracheal pressures. It is felt that the lower lobes in these cases developed hypostatic edema while standing, prior to actual use in the perfusion circuit.

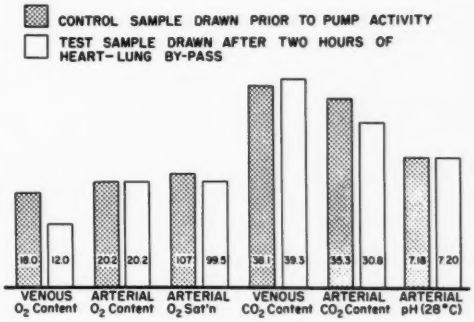
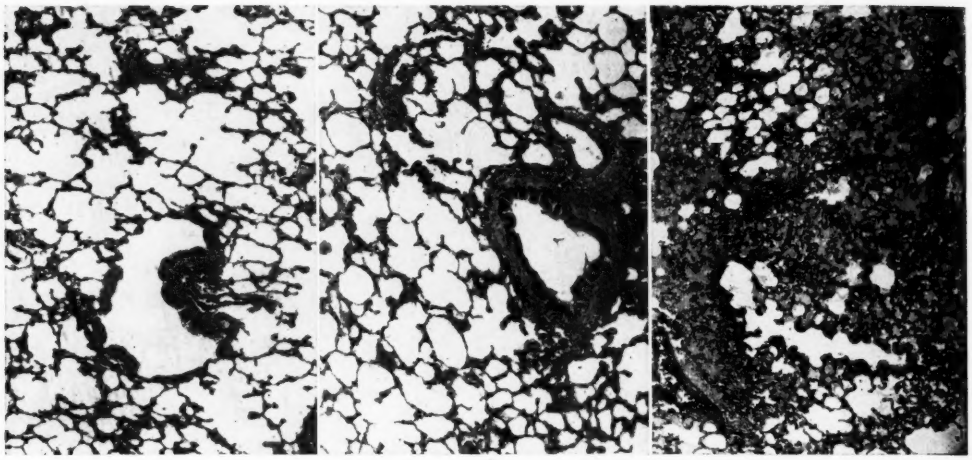


Fig. 5. Gas analyses of whole bloods. All O_2 and CO_2 contents are plotted in volumes per cent. Oxygen saturation is expressed in terms of per cent.

It should be pointed out here that even massive pulmonary edema in homologous donor lungs does not necessarily preclude their use in heart-lung by-pass. Since these lungs are discarded after the by-pass is discontinued, the respirator pressures can be safely raised to 40 to 50 centimeters of water. At these pressures, gaseous exchange is normal and extravasation of fluid into the alveoli is suppressed in fresh homologous lungs. These pressures are not great enough to produce arterial "air" embolism.

It was noted in all experiments of the present series that the arterial blood delivered to the animal was bright red in color, suggesting excellent function of the homologous



a b c

Fig. 6. Photomicrographs of dog lungs. a, Section of a normal dog's lung following artificial respiration. b, Section of a dog's lung that had been used for a period of 2 hours to oxygenate homologous blood during heart-lung by-pass; this lung compares favorably with that in a. c, Section of a dog's lung that had been perfused with fresh heparinized human blood (containing no other anticoagulant) for a period of 20 minutes; note the presence of severe pulmonary edema, congestion, and intrabronchial bleeding.

lungs as regards gaseous exchange. Gas analyses of whole blood samples drawn immediately prior to and after 2 hours of heart-lung by-pass confirmed this impression. Figure 5 shows the results of gas analyses in 1 of the experiments. Oxygenation and carbon dioxide removal were well handled by the donor lungs.

After the by-pass was discontinued, the donor lungs were carefully examined. Nearly all lungs showed some degree of edema in the lower lobes but adequate gaseous exchange was maintained during the period of each perfusion at moderate endotracheal respirator pressures. Microscopic examination of the donor lungs after the by-pass revealed minimal extravasation of fluid into the alveoli of the lower lobes and absence of any edema in the upper lobes in four experiments. In 1 experiment moderate pulmonary edema was seen in the lower lobes with clear upper lobes (see Fig. 6).

RESULTS AND POSTOPERATIVE OBSERVATIONS

After preliminary experiments were done, a series of 5 consecutive experiments was conducted. In each experiment the heart and lungs of the experimental animal were by-passed during occlusion of the main pulmonary artery, for a period of 2 hours. All 5 animals recovered quickly, being able to walk on all four extremities 12 hours postoperatively. None of this series developed postoperative infection. Within the first postoperative week, all animals had regained their preoperative behavior and activity. The animals were followed clinically and with laboratory aids. Figure 7 is a graph showing the average values of determinations of free plasma hemoglobin and the hematocrit in the consecutive series. The maximum average rise of free plasma hemoglobin was 110 milligrams per 100 cubic centimeters of plasma which occurred *24 hours after operation*. The plasma hemoglobin remained elevated for 3 days; this elevation was associated with an average drop in the hematocrit to 35. These findings indicate that the mechanical pumps damage and, thereby, decrease the survival time of a significant, but not dangerous, number of red blood corpuscles.

Complete blood counts and serum electrolyte determinations were done. Table I

TABLE I.—REPRESENTATIVE VALUES FOR BLOOD COUNTS AND SERUM ELECTROLYTE DETERMINATIONS

Time	Hct. % RBC	Hgb. gm. %	RBC m/cu. mm.	WBC No./ cu. mm.	Differential				Platelets T/ cu. mm.	Plasma hgb. mgm.%	Serum Na mEq./L.	Serum K mEq./L.	Serum Cl mEq./L.	Serum CO_2 mEq./L.	Total protein gm.%	Albumen gm.%	Blood volume c.c.
					P	L	M	E									
Preoperative	44	15.2	5.7	9,000	60	23	7	14	234	1.5	143	4.1	108	22	6.6	4.0	1,300
2 hours by-pass	51	15,8	6.7	6,000	75	19	1	7	124	62	143	3.5	...	22	6.4	3.7	.....
Postoperative	44	....	..	.....	..	..	..	..	...	52	140	4.1	100	18	5.8	3.7	1,340
PO 1	41	12.7	5.2	26,600	92	5	4	0	82	55	144	4.2	105	17	6.3	3.4	1,500
PO 3	25	9.2	4.0	15,800	84	8	4	4	114	1.5	146	4.6	106	21	5.7	3.2	1,300
PO 12	33	11.2	4.5	17,900	80	11	10	2	280	..	147	4.6	111	21	6.4	3.5	1,500
PO 150	43	14.0	5.8	11,300	67	14	6	15	380	..	146	5.5	105	23	6.5	2.8	....

shows representative values for these determinations up to the fifth month after operation. In this particular animal the hematocrit drop was the largest of the entire series (25 on the third postoperative day) yet showed relatively low values for free plasma hemoglobin (maximum of 62 mgm. per 100 c.c. of plasma). Blood volume determinations remained constant within the limits of accuracy of the method (Evans blue). Hemoglobin determinations and red blood corpuscle counts paralleled the hematocrit value. The white cell count showed a temporary rise (granulocytic) during the first 2 weeks after operation. The platelets decreased to 35 per cent of the preoperative level on the first postoperative day but the animal exhibited no bleeding tendency. The platelet count was normal on the twelfth day after operation. This animal exhibited the greatest drop in the platelet count in this series. Serum levels of sodium, potassium, and chloride ions and carbon dioxide content showed no significant variation during the period of observation. The values for plasma proteins showed no significant change.

The animals exhibited no untoward symptoms after operation with the exception of early transient weakness that compared favorably in duration and degree with that seen in animals subjected to intra-abdominal procedures. Postoperative accumulations of both air and blood in the chest were minimal and did not require thoracenteses after operation. One animal died of distemper during the ninth postoperative week. Necropsy revealed severe respiratory distemper. Three animals were sacrificed in health at 7, 6, and 5½ months after operation respectively. The fifth animal is alive and very active with no untoward symptoms 8 months after operation. Careful necropsy of the 4 dead animals revealed the following pertinent findings. All animals showed left lung adhesions to the thoracotomy site. The pericardium had been left open at the time of operation; at the time of death pericardioepicardial adhesions varied from none to general, loose, nonconstricting synechias. The brachial artery cannulation site in all animals was well healed. In 3 animals there was a small hard endothelialized nodule in the lateral wall of the right atrium between the orifices of the inferior and superior venae cavae. There was no constricting effect by these nodules. The latter finding suggests that more gentle vacuum could be applied to the right pump reservoir during by-pass; i.e., less than 40 millimeters of mercury. The myocardium showed no gross evidence of scar or other injury. With the exception of the animal that died of distemper, all lungs were grossly normal. All other organs, including liver, kidney, spleen, adrenal gland, gastrointestinal tract, urinary bladder, skeletal muscle, and brain, were grossly normal.

At necropsy, specimens of various tissues were taken for histologic examination. Sections were made in each animal of the left

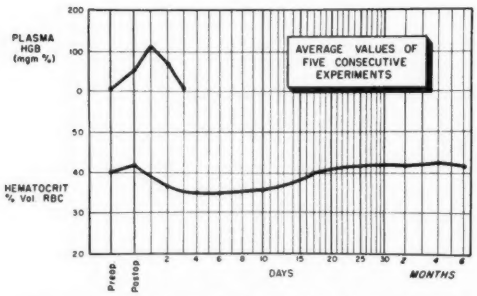


Fig. 7. Graph of hematocrit and free plasma hemoglobin levels following heart-lung by-pass (see text).

ventricle, right ventricle, lateral right atrial wall, both lungs, liver, kidney, spleen, adrenal gland, urinary bladder, skeletal muscle, left brachial artery cannulation site, cerebrum, internal capsule and basal ganglia, pons, and cerebellum. Microscopic examination of all these tissues revealed no marked or insidious changes in microscopic architecture or cellular detail with the following exceptions. The animal that died of respiratory distemper showed massive bilateral acute pneumonitis, and the right atrial nodules of 3 animals on microscopic study showed a local scar with calcification. The nodules were well covered with endothelium and probably represented old subendocardial collections of a small amount of blood secondary to injury from the right atrial cannula at the time of by-pass.

DISCUSSION

This method of heart-lung by-pass is not proposed for use in the human subject, although further work in this direction may demonstrate some usefulness for this purpose. On the other hand, this method is practical in the laboratory for various studies requiring heart-lung by-pass, for fresh homologous lungs as efficient extracorporeal oxygenators are easily obtainable and economical in that an animal used as a blood donor can serve also as the lung donor. Although the number of experiments in the present series is small, the results are consistent and reproducible. At the present time we are using this method of by-pass to enable a more detailed study of cardiac and circulatory physiology and also to study various experimental intracardiac procedures. For instance, 2 animals were subjected to left atriotomy during heart-lung by-pass. In both animals it was shown that the mitral valve could be exposed to direct vision and easy accessibility, that the left ventricle could be filled with air and subsequently refilled with blood with prevention of air embolism after the by-pass was discontinued, and that the amount of blood returned to the left atrium via the bronchial circulation was negligible as regards blood loss in the normal dog during heart-lung by-pass.

During heart-lung by-pass three chambers of the heart are essentially devoid of blood. These three chambers are the right ventricle, the left atrium, and left ventricle. If the bronchial return were sufficient to interfere with a particular study, it could be quantitatively aspirated by connecting a cannula placed within the left atrium to a sidearm in the input lead of the left (or right) pump. If an experimental procedure on the heart involved the right atrium, then the cannula described by Leeds or by Sewell and Glenn could be used in place of the right atrial cannula described in this communication.

Whereas homologous lungs have been found to be useful within 5 hours of death of the donor animal, heparinized and exsanguinated homologous lungs stored under refrigeration for 18 to 24 hours developed congestion and massive pulmonary edema immediately upon institution of perfusion. This is in agreement with the findings of Potts. Likewise, lungs of various species perfused with heterologous blood developed acute congestion with massive pulmonary edema. We have perfused pig and sheep lungs with dog blood, and dog lungs with sheep, pig, and human blood; all failed (Fig. 6). All bloods were heparinized and contained no other anticoagulant. The mechanism of the failure of heterologous lungs is not clear, but the site of incompatibility is probably in the capillaries (and alveoli). As much as 2 liters of blood can be pumped into the pulmonary artery of the heterologous (and stored homologous) lungs without increase in the pulmonary artery pressure, with little or no pulmonary vein outflow,

and with massive endotracheal accumulation of edema fluid which was identical with plasma on chemical evaluation. During 1 experiment the heart and lungs of an experimental dog were by-passed using simple pumps and a freshly gathered set of sheep lungs. This by-pass was continued for 30 minutes; during this period the return of blood from the sheep lungs was very poor, averaging 200 cubic centimeters per minute; 2,600 cubic centimeters of blood were infused into the system during the perfusion. Most of this blood did not get through the sheep lungs. The animal remained in shock during the length of the perfusion. The fact that the animal recovered completely from the procedure is a tribute to the sturdiness of this particular experimental dog. From these pilot studies it is felt that until more is known about the mechanisms of incompatibility of heterologous tissues, heterologous lungs will have no value as extracorporeal oxygenators. However, the use of stored homologous lungs, in our opinion, warrants further study.

SUMMARY

A method of heart-lung by-pass using simple mechanical pumps and fresh homologous lungs is described.

Five dogs, in a consecutive series, were each subjected to a 2 hour period of heart-lung by-pass combined with occlusion of the main pulmonary artery. All 5 dogs recovered from this procedure without developing postoperative complications. Physiologic data obtained during these 5 experiments are presented.

This procedure of heart-lung by-pass has been successfully applied to more than 25 dogs in subsequent experiments dealing with further studies of cardiac and circulatory physiology.

The present inadequacy of using stored homologous lungs and heterologous lungs as extracorporeal oxygenators is discussed.

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EDITORIALS

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DECEMBER, 1952

UNDERGRADUATE TEACHING IN SURGERY

SURGERY in the medical undergraduate curriculum implies very much more than the performance of a surgical operation. The operative procedure per se is only an incident in a course of treatment, the success of which depends upon careful attention to diagnosis, preoperative care, and postoperative care. No one will doubt that diagnosis should entail a careful history, a complete physical examination, and adequate use of appropriate laboratory aids. In the teaching program of all British medical schools emphasis has always been placed upon history-taking and physical examination. This has applied in the surgical department of most of those schools just as in the other clinical departments. The result of this emphasis on practical clinical training has been that British graduates have been superior bedside clinicians. On the other hand, in the North American schools in recent years there has been a trend toward the emphasis of science in undergraduate teaching. This has applied particularly to the surgical departments of our medical schools. Many of our final year students when confronted with a patient will outline in detail the various laboratory procedures indicated in the investigation of any surgical patient before they will take a careful history and do an accurate, complete, time-consuming physical examination. This has resulted from the overemphasis of science in our teaching in surgical departments rather than stressing the importance of bedside history-taking and careful physical examination. There are deficiencies in both these extremes and it is to be hoped that we may find a middle course which will embody the best aspects of both types of teaching. We will all agree that the ideal medical graduate is the one who will be taught to take a careful history and do a methodical physical examination in the best Oslerian style but at the same time will be trained to augment these investigations with the scientific laboratory aids essential to complete his diagnosis.

There can be no doubt that many surgeons interested in the teaching of surgery have been concerned as to whether or not they are adequately preparing graduates to perform surgical procedures that they are obliged to carry out in general practice. It is the feeling of some that participation by final year students as clinical clerks and by junior interns in many of the superradical operations is not adequate preparation for the type of surgery they will be expected to do in their early years of practice. If, as teachers of surgery, we made a concentrated effort to see that our medical graduates became competent in the various operations considered general practice

procedures they would be well qualified surgically for general practice. Apprenticeship in some form has been reinstated and unquestionably it has some advantages over other teaching methods. Many of the benefits of this type of training, particularly in minor surgery, cannot be equalled in large teaching hospitals with their multiple specialty services. It is to be hoped that it will be given a fair and adequate trial under carefully chosen preceptors.

There has been some question in the minds of others as to whether or not we should limit the import of the medical degree as far as surgical qualifications are concerned. In other words, today when we license a doctor we license him to carry out any surgical procedure that he may choose to do. One might argue that we should license the graduate in a limited manner to do only the surgical operations considered those of general practice. Upon receiving further training his scope could be enlarged commensurate with his added training. We would then be obligated to provide training centers for them to broaden their field at an opportune time. Today the medical graduate in many instances continues his training immediately upon graduation and consequently there is not always the opportunity for the man who has been doing general practice to return to the surgical training center. These thoughts relative to general practitioner training do not apply to those medical schools where the preparation of general practitioners is not of primary importance. In heavily populated areas, particularly in the eastern part of our continent, the general practitioners may not be required to carry out emergency surgical procedures but in many other sections it is their responsibility and theirs alone to take care of many acute surgical emergencies. It is our function, therefore, to see that they are efficiently trained.

Surgical teachers have been chosen in many instances because of their research ability or their ability as clinicians, not often because of their ability as teachers. Is it not time we appointed teachers on the basis of their ability to teach? WALTER C. MACKENZIE.

HYPOGASTRIC VENOUS PLEXUSES ABOUT THE SCIATIC NERVE IN EXTENDED PELVIC NODE EXCISION AND PELVIC EXENTERATION

THE recent interest in major excisional procedures for pelvic cancer raises certain features of operative technique and gross anatomy in the living subject that are worthy of discussion. In the classical combined abdominoperineal resection of the rectum, total cystectomy, and radical hysterectomy (so-called Wertheim operation), the regions immediately overlying the large nerve trunks of the sacral plexus that join to form the sciatic nerve in the posterior lateral portions of the pelvis receive scant if any attention because according to the usual manner of performing these operations these regions are not exposed or dealt with in any detail.

Cancer of the cervix spreads, among other pathways, backward along and in the uterosacral ligaments. This is observed upon rectovaginal examination in these patients when "tightening" and shortening of these ligaments is readily appreciated. Clinically, this mode of extension manifests itself by severe pain in the pelvis and sciatic nerve type of radiation down one or both legs.

The purpose of the radical hysterectomy and lymph node excision, as previously described,[1] is to encompass widely the primary lesion and those tissues to which spread is

[1]BRUNSCHWIG, A. The operative treatment of carcinoma of the cervix. Am. J. Obst., 1951, 61: 1193.

known to be likely to occur. Metastases and direct extension to the hypogastric groups of lymph nodes and areolar tissues surrounding them necessitates that these nodes and tissues be removed. A review of the standard text anatomical descriptions does not permit the surgeon to get sufficient information concerning what he will here encounter. After division of the hypogastric artery near its origin, or perhaps 2 or 3 centimeters distal to its origin and retraction of the upper and lower segments, the main trunk of the hypogastric vein will be exposed. This vein varies considerably both as to size and number of its branches. It is usually thin walled and easily entered inadvertently, when lymph node and areolar excision is carried out in the posterior lateral portions of the pelvis. Bleeding then will be brisk and copious unless the branches are rapidly secured. From the deep surfaces of the hypogastric vein there are branches varying in number and distribution which insinuate themselves between the large nerve trunks that make up the sciatic nerve. Attempts to clamp these blindly may easily result in clamping the sciatic nerve roots. Once divided or torn, the distal ends of these branches retract deeply between the sciatic nerve roots or even behind them. If they cannot be easily secured with hemostats, time should not be lost in repeated attempts to secure them in the face of vigorous hemorrhage. The latter can usually then be controlled by gauze packs soaked in hot saline and applied to the region with pressure. While this pressure pack is applied other phases of the operation can be carried out.

With pelvic cancer there is often congestion of the pelvic blood vessels, and this includes not infrequently a marked dilatation of the branches entering the hypogastric vein.

It might be pointed out by others that difficulties in the regions described have not been encountered by them in the performance of large pelvic operations, especially the extended radical hysterectomy and pelvic node excision or pelvic exenterations. In reply to this the writer points out that in all probability the lymph nodes and areolar tissues over the sciatic nerve roots were not systematically excised so that at the termination of the operation the sciatic nerve roots were not laid bare. If the sciatic nerve roots are not denuded of overlying tissues and are not laid bare at the termination of the pelvic lymph node excision, then pelvic lymph node (and areolar tissue) excision is not carried out as meticulously as it might be. Whether or not this phase of the operation is necessary or justifies itself, cannot at this time be determined. But if extended pelvic lymph node and areolar tissue excision is envisaged then this phase of the operation should be carried out, especially, as indicated previously, since cancer of the cervix (and possibly lower pelvic colon) spreads to this parasciatic nerve region. Gross anatomy, especially in the living subject on the operating table, is not yet an absolutely static subject but in certain details, especially associated with disease, there are some conditions that surgeons may not yet generally appreciate until they operate in regions not commonly dealt with in the past.

ALEXANDER BRUNSCHWIG.

THE SURGEON AT WORK

USE OF THE PLASTIC INTRAVENOUS CATHETER FOR MULTIPLE AND MASSIVE TRANSFUSIONS AND PROLONGED INTRAVENOUS FLUID THERAPY

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Miami, Florida

WITH the increasing use of massive and multiple blood transfusions and parenteral fluid therapy, improved methods for their rapid and continuous administration are necessary. The plastic intravenous catheter helps to meet these requirements, but it has not been as generally employed as is justified. It is the purpose of this paper to review the indications and advantages of the intravenous catheter and briefly to describe the methods of its insertion.

Among the reasons for the slow acceptance of the intravenous catheter for transfusions is the apparent lack of realization by some physicians of the urgency for complete restoration of blood volume in hemorrhage and shock, and for the necessity of continually maintaining a normal blood volume in severely burned patients by the prolonged administration of plasma and whole blood during the critical first 72 hours. In these emergencies one or two catheters should be inserted early to facilitate adequate replacement therapy.

The postoperative shock, so frequently seen in the past, has almost been eliminated by the preoperative correction of the depleted blood volume in chronically ill patients requiring surgery and by the quantitative replacement of blood as it is lost during the operation. However, many patients are deprived of this adequate replacement therapy by minor technical difficulties in its administration, most of which may be prevented by the preliminary insertion of an intravenous catheter.

The intravenous catheter is extremely helpful in transfusing infants. Many pediatricians use it routinely to facilitate the administration of blood, plasma, and parenteral fluids in very sick or dehydrated infants and children. It is the method of choice for all exchange transfusions in hemolytic diseases of the newborn.

Severely anemic patients with normal blood volume or in whom an increase in blood volume is contraindicated may have their anemia rapidly corrected preoperatively by the administration of large or multiple cell suspension transfusions. This may be simplified by the use of an intravenous catheter.

In all cases of internal bleeding, such as ruptured ectopic pregnancy, esophageal varices, or bleeding of peptic ulcer, the exact amount of blood loss cannot be determined and the danger of continued or recurrent bleeding is great. The presence of an indwelling intravenous catheter may be lifesaving.

The metal cannula and needle are not well tolerated in prolonged usage as the tip traumatizes the vein, which causes thrombosis or perforation with extravasation, necessitating discontinuance of the transfusion and utilization of another vein. In an attempt to prevent such trauma it may be necessary for the arm or leg and foot to be immobilized for long periods of time. Immobilization is not well tolerated by the patient and it limits the necessary nursing care. With the catheter in place and securely taped to the skin, full movement of the limb is possible without mechanical trauma to the vein wall.

We have found it difficult always to have sterile plastic catheters available with the transfusion and intravenous sets in the hospital wards, emergency rooms, and first aid stations. This is due to the fact that some sets are prepared and autoclaved by the hospital and others are prepared and packaged by the manufacturer as expendable sets. In either case intravenous catheters are not routinely included. Occasionally a

From the Medical Research Foundation of Dade County, The Blood Bank of Dade County, The Jackson Memorial Hospital, Miami, Florida, and the U.S. Veterans Administration Hospital, Coral Gables, Florida.

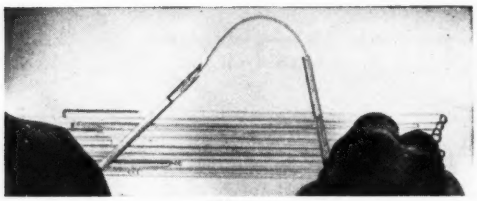

Fig. 1.

Fig. 1. Plastic intravenous catheter being removed from sealed glass tube containing 1:1,000 zephiran solution.

Fig. 2. Passing plastic intravenous catheter through 15 gauge needle previously inserted in vein.

Fig. 3. Withdrawing the needle from vein and retaining intravenous catheter in place by counterpressure over vein.

Fig. 4. A 19 gauge needle inserted into plastic intravenous catheter and joined to infusion or transfusion set.

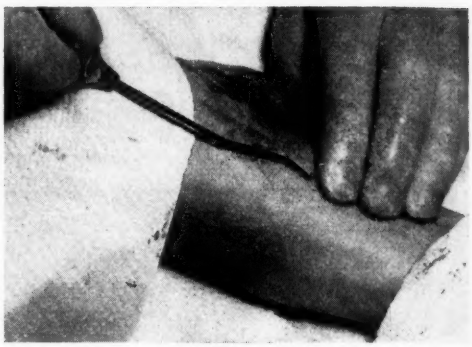

Fig. 3.

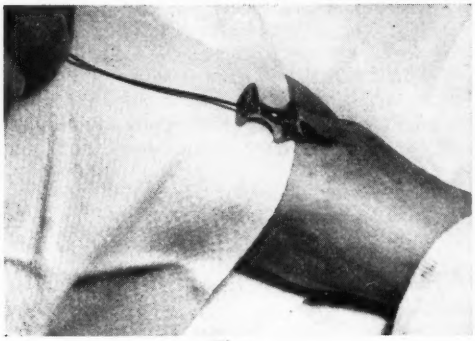

Fig. 2.

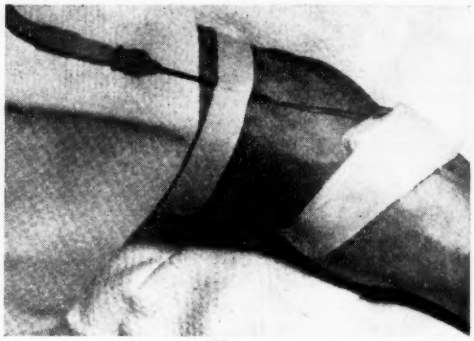

Fig. 4.

previously used and resterilized catheter is furnished by the hospital. It may be damaged and unusable, or if unused but resterilized it may be very stiff and pass through a large needle with difficulty, or lie tightly curved against the wall of a straight vein with some trauma to the intima.

The plastic catheters which we use are gas sterilized by formaldehyde and sealed in a glass tube containing a 1:1,000 solution of zephiran chloride (Fig. 1). This glass tube contains the sterile catheter ready for use. It requires no special handling and is furnished with the recipient set. The catheters are 8 inches long and of two diameters. The No. 19 catheter will pass through a 15 gauge needle and will accommodate a 19 gauge needle in its lumen. The larger No. 16 catheter is usually used for surgical insertion and it will accommodate a 16 gauge needle inserted into its lumen for the rapid administration of blood or plasma. These two sizes have proved adequate for our transfusion and intravenous fluid therapy.

METHODS OF INSERTION OF CATHETER

The method of insertion depends upon the accessibility of suitable veins for venipuncture. When the veins are adequate and it is desired to avoid repeated venipuncture in continuous or repeated replacement therapy, the catheter may be inserted through a large gauge needle.

The glass tube containing the intravenous catheter is cleansed with an alcohol sponge and broken in a sterile towel and the zephiran solution permitted to drain off. A 15 gauge needle attached to a small hypodermic syringe is inserted into a suitable vein. The tourniquet is removed and the extremity draped by a sterile towel extending under the needle hub. The syringe is detached from the needle and the catheter is then passed through the 15 gauge needle into the vein for approximately one-half its length (Fig. 2). The 15 gauge needle is then withdrawn using counterpressure with the fingers over the vein to hold the catheter in place (Fig. 3). The 19 gauge needle on the infusion set is then inserted into the end of the catheter (Fig. 4). The catheter is firmly se-

cured by adhesive tape to the skin. A small gauze dressing is applied to the puncture wound.

If the catheter fits too tightly in passage through the 15 gauge needle it may be grasped by hemostats at each end and stretched, thereby decreasing its diameter for easy passage through the needle. The ends crushed by the clamps may be cut away by sterile scissors.

In many instances veins are not available which will accept a 15 gauge needle, still it is desirable to use the intravenous catheter for blood or fluid administration. This may be the case in pediatric patients, in obese women, and in many others in whom the veins are small and inaccessible, or are collapsed as in shock. In such a case a suitable vein is exposed surgically and the catheter is inserted directly into the vein (Fig. 5). For this purpose the larger No. 16 catheter is used.

Usually a medial malleolar or antecubital vein is selected. In infants the great saphenous vein may be used. The skin is prepared and following novocain infiltration a skin incision is made obliquely across the vein and deepened to expose it. It is freed with a small hemostat. A fine silk or cotton suture is passed below it distally and ligated, and another is loosely placed under the vein proximally for traction to prevent bleeding as the vein is opened. The vein is incised transversely with a scalpel or scissors, and the catheter is inserted proximally into the vein for half its length. The proximal silk ligature is then tied securely about the vein and catheter. We have found that plain catgut ligatures may loosen after a few days and allow leakage about the catheter. The wound is closed with sutures and a small dressing is applied. The catheter is firmly attached to the skin by adhesive tape, and the infusion set is attached by inserting a blunt nosed 16 gauge needle into its lumen.

In order to close and retain the catheter in place between transfusions when continuous drip is not desired, several methods may be employed. A small hypodermic syringe containing physiologic saline may be firmly attached to the needle in the catheter. The saline is then injected to expel blood from the catheter, the plunger secured and taped to the skin. We have in this manner used catheters for daily transfusions or for obtaining daily blood specimens for periods of 2 weeks or longer. An alternate method of plugging the catheter temporarily is to attach a Luer-Lok plug to the needle or to remove the needle and crush the tip of the catheter with a hemostat and flame seal it. This sealed portion may be cut away with sterile scissors when it is desired again to utilize

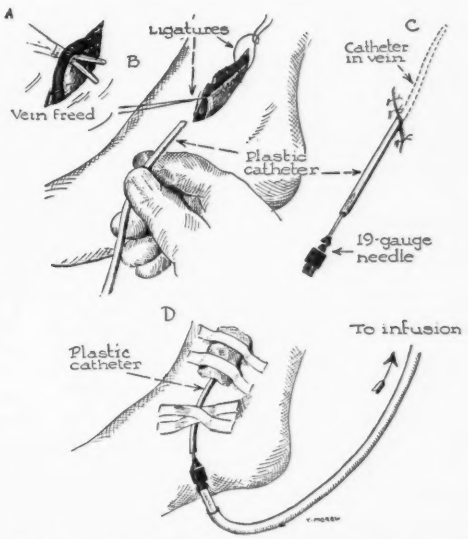

Fig. 5. Surgical insertion of plastic intravenous catheter by "cut down" method.

the catheter. It is always well to inject normal saline through the catheter before sealing.

We have occasionally noticed irritation after as early as 4 or 5 days of use when concentrated solutions, irritating medications, and amino acids are administered through the catheter. We have noted this more frequently when a large catheter is forced into a small peripheral vein. With the use of the larger veins the patients seldom experience local reaction. When this does occur it will subside promptly upon discontinuing its use.

SUMMARY AND CONCLUSIONS

The indications, advantages, and various methods of using the plastic intravenous catheter are presented.

The intravenous catheter is a valuable adjunct to the success of rapid, massive, and multiple transfusions and continuous intravenous fluid therapy.

It should be immediately available for use as an essential component of the expendable and nonexpendable transfusion administration equipment.

The previously sterilized polyethylene or polyvinyl plastic intravenous catheter of proper gauge and length, sealed in a glass tube containing 1:1,000 zephiran solution, appears most suitable for universal use.

THE SURGEON'S LIBRARY

REVIEWS OF NEW BOOKS

EVERY student of medicine is familiar with the name of Galen, and realizes vaguely that he practiced medicine about 1800 years ago. Perhaps he knows also that Galen was a prolific writer, often verbose and quibbling. His real place in medicine is realized by only a few.

The most reliable information indicates that Galen was born at Pergamus in Asia Minor in 161 A.D. He began the study of medicine when he was but 17 years of age. Through the following years he sought learning wherever he could find it; he travelled to any region or country where he thought he might increase his knowledge. At the age of 32 he went to Rome and soon received recognition by men of prominence. At the age of 37 he returned to Pergamus, but the Emperors Marcus Aurelius and Lucius Verus recalled him. After a long and interesting career he is supposed to have died at the age of 70.

Galen had an excellent education, not only in medicine but in philosophy and literature. He had a rather extensive knowledge of anatomy and made detailed dissections. He was an astute observer and recorded his observations and conclusions. It is believed that 500 books on medicine written by him can be accounted for, and "half as many on other subjects.' Some of these were lost during his lifetime in a fire.

His writings were voluminous. He was critical of other physicians, at times almost insulting, but remained ever true to Hippocrates. Galen was more than 1,000 years ahead of his time so far as medicine is concerned. Many descriptive words and phrases used by him are in common use today, words such as sanguinic, phlegmatic, choleric.

In his book, *Hygiene*,[1] a variety of subjects are discussed. The material has been divided essentially into the art of preserving health, exercise and massage, bathing and fatigue, forms and treatment of fatigue, diagnosis, treatment and prevention of various diseases, and prophylaxis of pathological conditions.

Types of massage and exercise including the external use of oils and with consideration of temperature are discussed in great detail. Many of his conclusions are remarkable. He states, "Those children who are nourished by the mother's milk enjoy the most appropriate and natural food. .. The habit of the mind is impaired by faulty customs in food and drink and exercise and sights and sounds and music." He stressed cleanliness of the infant. He taught that perspiration contained an excrement of the body. He discouraged the use of drugs when natural means did as well or better. He recognized the fact that poor pasturage resulted in unsavory milk unsuitable for use. In chronic constipation he condemned purges and recommended oil injections. Such are only a few of his teachings almost 2,000 years ago.

Pages and pages are given over to quibbling with Theen about massage, all to no purpose that can be discerned. He says, for example, "Theen, the Alexandrian (who) handled the whole subject best for he wrote four volumes about exercise in detail; all of which I might have said too, being better qualified than he to interpret."

This little volume affords interesting reading. It is a work which demonstrates a man's tremendous enthusiasm and ability as well as his shortcomings. Galen worked with the crudest of equipment and compounded his own drugs. The deductions he made 1,800 years ago are surprising and many still are accepted as basically correct.

JOHN A. WOLFER.

THE book entitled *Management of the Newborn*[2] by Arthur Hawley Parmelee reflects a well organized and orderly collection of keen clinical observations well tempered with a broad honest appraisal. Dr. Parmelee describes and evaluates in an applicable way simple clinical points that even the neophyte physician has seen but possibly not properly categorized. The management of the newborn and premature is covered in a nondetailed approach that makes this publication a good review for the experienced pediatrician. The method of handling the material presented would also make the book valuable reading for the medical student or nurse who wished to cover the subject in one short volume. Sufficient references are given for the individual who wishes to delve more deeply into the subject.

L. MARTIN HARDY.

IN the second edition of the monograph, *Vascular Diseases in Clinical Practice*,[3] Dr. Wright has presented an excellent discussion of the peripheral

[1] A Translation of Galen's Hygiene (De Sanitate Tuenda). By Robert Montraville Green, M.D. With an Introduction by Henry E. Sigerist, M.D. Springfield, Ill.: Charles C Thomas, 1951.

[2] MANAGEMENT OF THE NEWBORN. By Arthur Hawley Parmelee, M.D. Chicago: The Year Book Publishers, Inc., 1952.

[3] VASCULAR DISEASES IN CLINICAL PRACTICE. By Irving Sherwood Wright, M.D. 2nd ed. Chicago: The Year Book Publishers, Inc., 1952.

vascular diseases based upon his extensive investigative and clinical experience.

The first chapter contains a complete classification of the subject. This is followed by a chapter in which the methods of examination and the diagnostic tests are described and evaluated. In the succeeding chapters the various conditions are discussed thoroughly, beginning with a historical review and continuing with the pathology, diagnosis, and treatment. The greatest part of the book rightfully deals with the diagnostic methods and the discussions of the more common diseases met in practice, but the rare vascular disturbances are not overlooked and are described briefly but adequately. The sections on atherosclerosis, anticoagulant therapy, and the shoulder girdle syndromes were revised and enlarged in this edition to include the latest views on those subjects. An extensive bibliography relative to the subjects discussed follows each chapter. All the material is presented from the viewpoint of the internist dealing with these conditions and the surgical aspects of the treatment are mentioned only briefly. In a final chapter the author discusses the medicolegal and industrial aspects of peripheral vascular diseases.

The book is well written on fine paper and has numerous photographs and charts to illustrate the points made in the text. It should make a worthwhile addition to the library of the internist and surgeon. SAMUEL PERLOW.

THE rather small delightful but brief, 176 page account, of *The Life and Work of Astley Cooper*[1] was written by a Guy's Hospital surgeon, because the author felt that this famous English surgeon was not as widely recognized as he should be. The material is, of course, far less complete than the 2 volume biography by Cooper's nephew, Bransby Cooper (1843), but is far more likely to be widely read.

The author recounts the professional life of Cooper in a most charming and appreciative manner. The contributions of Cooper are reviewed in some detail, most attention being given to his work on hernia, fractures and dislocations, and his vascular surgery. His sustained intense interest in anatomy and experimental work are praised and credit is given for his achievements. Cooper is depicted as a gifted genius who worked very hard for 50 years to achieve fame and fortune as a teacher, surgeon, and researcher. An assiduous anatomist and experimenter, he continued his writing and dissecting even after retirement from hospital work.

Cooper's bibliography and a list of references, as well as a short index, are included in the volume. Fourteen illustrations are presented which include some of Cooper's engravings.

This volume should interest every medical student and more particularly students of surgery, for it presents in an entertaining fashion the prescription for success used by Astley Cooper which, so far as this reviewer is concerned, is as true today as it was 150 years ago. THOMAS C. DOUGLASS.

[1]THE LIFE AND WORK OF ASTLEY COOPER. By R. C. Brock, M.S., F.R.C.S., F.A.C.S. Edinburgh, London: E. & S. Livingstone, Ltd., 1952.

THE seventh edition of Professor Bell's well known *Text-Book of Pathology*[2] is attractively bound and printed, well illustrated with excellent photographs, and not excessively bulky. Pathology is presented in a systemic fashion in 14 chapters devoted to general pathology and 16 chapters on the special pathology of the different organ systems. A good balance has been maintained between important and common diseases and those which are unusual. The chapter on nephritis is exceptionally good. The book should be most helpful to medical students, residents, and practicing surgeons and physicians who need a handy reference book to the facts of pathology. WILLIAM B. WARTMAN.

THE volume *Archiv und Atlas*[3] presents a wide variety of normal and pathological conditions. The roentgenograms are shown as positives and reproductions are for the most part sharp and clear. Line drawings explain the anatomy well. The work indicates that much care, precision, and thoroughness went into its preparation. Some of the smaller illustrations, however, show little detail.

The text, in German, is concise but adequate. Findings in the common diseases of the ear, nose, and throat are presented in logical order. With films of illustrative cases there are brief descriptions and short historys of the disease and its course. The position of the patient, x-ray tube, and film for various views are clearly shown.

The atlas is a valuable practical reference book for x-ray study of pathology of the ear, nose, and throat. It should prove quite useful to the practitioner and specialist. THOMAS GALLOWAY.
JOHN ELSEN.

IN recent years a number of investigators in the United States and Europe have been endeavoring to adapt to the human brain the stereotaxic instrument of Horsley and Clarke which has been so useful in producing lesions within the interior of the brains of cats and monkeys. By this means it is hoped that discrete lesions may be made accurately in the subcortical fiber tracts, the brain stem, the thalamus, and the basal ganglia without injury to the overlying cerebral tissues. It seems likely that such methods would be most useful in neurophysiological studies, and in the treatment of mental disorders, painful states, abnormal involuntary movements, and deep seated tumors.

[2]A TEXT-BOOK OF PATHOLOGY. By E. T. Bell, M.D. Contributors: B. J. Clawson, M.D., and J. S. McCartney, M.D. 7th rev. enl. ed. Philadelphia: Lea & Febiger, 1952.

[3]ARCHIV UND ATLAS; DER NORMALEN UND PATHOLOGISCHEN ANATOMIE IN TYPISCHEN ROENTGENBILDERN; DIE KRANKHEITEN DER NASENNEBENHOEHLEN, DER OHREN UND DES HALSES IM ROENTGENBILD. By Prof. Dr. Richard Mittermaier. Stuttgart: Georg Thieme, 1952.

These studies in various neurological centers began almost simultaneously and largely independently. Spiegel and Wycis were among the first investigators and they wrote *Monographs in Biology and Medicine; Stereoencephalotomy (Thalamotomy and Related Procedures)*[1]. However, their assertion that the works of the others have been "modifications" of theirs and the implication that these other investigators were all originally stimulated to concentrate on this subject by the 1 page article by Spiegel, Wycis, Marks, and Lee published in *Science* in 1947 is hardly in accord with the facts.

The great problem in this field is the precise localization of various structures within the human brain. This difficulty is the result of the great variability in the sizes and shapes of human heads and brains, and the difficulty in securing, for the preparation of an atlas, well preserved normal brains without shrinkage or swelling. It is also difficult and important to preserve the size and shape of the brain being studied after it is removed from the head and while it is being sectioned, embedded, cut with the microtome, stained, and mounted. These authors claim to have circumvented these difficulties.

Spiegel and Wycis have used the calcified pineal body as seen in plain roentgenograms of the skull or the posterior commissure as determined by pneumoencephalography as their point of fixation from which they have measured the position of all other intracerebral structures in which they were interested. However, one learns from their tables that the distance between structures as close together as the pineal body and the posterior commissure varies from 4.5 to 8 millimeters sagittally and from 1.3 to 3.5 millimeters vertically. The measurements to other more distant structures vary even more. It thus is difficult to see how anything approaching the accuracy needed in this field is achieved by this method. These difficulties are graphically demonstrated by comparing some of the authors' own photographs of the brains which were used for this study. If, for example, one compares Figure 29, page 49, a section made 30 millimeters anterior to the pineal gland, with Figure 39, page 69, a section made 29 millimeters anterior to the pineal gland, the differences are striking. Figure 39 shows a sizable part of the anterior and ventral anterior nuclei of the thalamus while Figure 29 shows none of the thalamus whatsoever. If one compares Figure 35, page 61, "through the center of the pineal gland," and Figure 51, page 93, "through the pineal center," one sees considerable differences. Figure 51 shows a large section of the medial geniculate body, Figure 35 shows none. The contour of the pulvinar is quite different in the two figures. There is no connection between the anterior colliculus and the thalamus in Figure 35; there is in Figure 51. These distinctions must make a difference in the localization of lesions made if one were using these plates. Other workers have found it necessary to make different atlases for heads of various sizes and shapes. It seems questionable if Spiegel and Wycis have satisfactorily surmounted this difficulty. In view of the crude methods necessarily used in preparing these brains and plates and making these measurements, such measurements as "18.3 millimeters anterior to the center of the pineal gland," and "3.9 millimeters in front of the center of the posterior commissure," would seem of very dubious value. One is also reminded of the difficulties in determining with any degree of accuracy the center of the pineal body from plain roentgenograms of the skull and of the posterior commissure from pneumoencephalograms.

The authors' check upon the accuracy of the placement of their lesions has been determined largely from postoperative roentgenograms of the skull which show the position of droplets of pantopaque injected at the time of operation into the sites of the electrolytic lesions. The inadequacy of such controls is obvious. Four postmortem studies are briefly presented but the data supplied both in the text and the illustrations are not sufficient to judge the accuracy of the method even in these 4 cases (over 100 patients have been operated upon).

In spite of the difficulties which are inherent in this worthwhile task and which the reviewer has emphasized, this is a most meritorious endeavor and warrants much encouragement. This atlas has been well reproduced, well labelled, and documented. It will be a high target at which those who follow must shoot. It will be an essential book to all who wish to use the methods of Spiegel and Wycis and to all who would pursue this line of investigation.

We could not agree with the authors that "the method is beyond the experimental stage" as to technique, application, or results. It is rather to be hoped that this is only the bare beginning in a vast field of human neurophysiology and neurological therapeutics. PAUL C. BUCY.

THE book entitled *Battle Casualties*[2] is unusual in that it has combined many interesting facts concerning the incidence, mortality, and the many considerations necessary in the treatment of battle casualties. It contains much statistical data gained from World War II. The wide variations used by the Armed Services in collecting such data are pointed out clearly and, as one reads this book, he is impressed with the necessity of correlating these reports. In future planning for treatment of battle casualties, the material contained in this book will be extremely useful and, this volume certainly will be indispensable for one who has to deal with the logistical planning for battle casualties. There is a splendid summary by Dr. Edward Churchill wherein he suggests a set of rules for the evacuation and

[1] MONOGRAPHS IN BIOLOGY AND MEDICINE. VOL. I. STEREOENCEPHALOTOMY (THALAMOTOMY AND RELATED PROCEDURES). Part I, METHODS AND STEREOTAXIC ATLAS OF THE HUMAN BRAIN. By E. A. Spiegel, M.D., and H. T. Wycis, M.D., F.A.C.S. New York: Grune & Stratton, 1952.

[2] BATTLE CASUALTIES; INCIDENCE, MORTALITY, AND LOGISTIC CONSIDERATIONS. By Gilbert W. Beebe, Ph.D., and Michael E. DeBakey, M.D. Springfield, Ill.: Charles C Thomas, 1952.

distribution of battle casualties. The entire book is a source of valuable information for anyone who must plan for the care of battle casualties.

HARVEY S. ALLEN.

THE first edition of the book entitled *Lehrbuch der Geburtshilfe*[1] appeared in 2 volumes in 1948. The author with the collaboration of Bickenbach, an obstetrician, and Droysen, the artist, has condensed the 2 volume book into one. This was accomplished both by reducing the amount of text and also by diminishing the size of the type, so that this book contains only two-thirds of what appeared in the first edition. In my opinion this edition is far better than the first edition. A considerable amount of extraneous and controversial material has been omitted, many discussions have been condensed, and numerous illustrations have been reduced in size without losing any of their teaching value. The section which was reduced the least was that dealing with contracted pelves because Martius believes a knowledge of the mechanism and conduct of labor in contracted pelves is very important even though at present cesarean section has greatly simplified the treatment of pelvic contraction.

The book has been completely rearranged into 7 sections as follows: pregnancy, labor, multiple pregnancy and multiple labor, puerperium, lactation, obstetric pediatrics, and hygiene of reproduction. In the 2 volumes of the first edition there were 1,025 illustrations and in the second edition there are 786, many of these in color as in the first edition.

In this edition the description and illustrations of external mensuration of the pelvic inlet are retained although it is doubtful if any real information is obtained from these measurements. The authors treat most cases of eclampsia which occur in pregnancy and the first stage of labor by symptomatic therapy. However, they advise a vaginal or abdominal cesarean section for severe eclampsia which occurs in pregnancy or in labor when the cervix is not dilated and there is no improvement under medical management and the patient has oliguria, changes in the eye grounds, beginning pulmonary edema, and circulatory collapse. In my opinion such patients are extremely poor surgical risks and should continue to be treated by medical management. The death rate in eclamptic women following cesarean section is much higher than that of conservative management even in the seriously ill cases.

Throughout the book there is evidence of the vast obstetric experience of Martius and his obstetric collaborator. Nearly all the teaching is conservative and in accordance with practice by leading obstetricians throughout the world. The illustrations are excellent, the paper is sturdy and the type is clear although somewhat small. The authors and publishers are to be congratulated again for having produced an outstanding book. J. P. GREENHILL.

[1]LEHRBUCH DER GEBURTSHILFE. By Prof. Dr. Heinrich Martius, Prof. Dr. Werner Bickenbach, and Käthe Droysen. 2nd ed. Stuttgart: Georg Thieme, 1952.

THE sixth edition of the *Textbook of General Surgery*[2], a rather well-known volume, is quite fittingly dedicated to Dr. Evarts A. Graham, whose inspiration to the editors is thus gracefully acknowledged. The authors of the various chapters are the same as those who contributed to earlier editions. This book makes its appearance 3 years after the fifth edition, and considerable differences are apparent in some chapters.

It is fascinating to reflect upon the changes that have come to pass within the space of 3 years. In the present edition a section on chemotherapy has been added and a chapter on vascular surgery has been provided. Material on the newer aspects of cardiac surgery has been added to the constantly expanding knowledge of thoracic surgery. There is emphasis on physiologic principles throughout the book, an emphasis which is very valuable, especially in the chapters on shock and burns.

It is a tribute to the resourcefulness of the authors that this much information could be compressed into a single volume, even though there are 1,110 pages. The work is directed more to the student than to the seasoned surgeon, and the information presented is that which the modern day medical student is required to know. In such a work the necessity for brevity is obvious, but well selected references are offered at the end of each chapter. It is gratifying to note how up to date most of the material is; the reader will come upon frequent references to aureomycin, terramycin, neomycin, and other agents only recently introduced.

The section dealing with bacteriology contains some data that also appeared in earlier editions; this is noticeable largely in matters of terminology, but it does not detract from the value of the work. The section on malignant neoplasms is broad in scope, a factor which obviously requires abbreviated descriptions. It is evident that the author of this section of the volume was not overly impressed with the "grading" of malignant tumors.

As would be true of any other book, it is inevitable that a surgeon, leafing through this volume, would find portions with which he would not be in complete agreement. Such a contingency actually is most desirable, for it is clear evidence of the constant shifting of viewpoints in the face of new additions to knowledge in an ever developing field.

The book will be of more value to the student and beginner than to experienced surgeons, because the authors have made a conscientious effort to include all important principles of surgery. For instance, much space is devoted to diseases of the bones, joints, skeleton, skull, tendons, ligaments, and nerves. At present (at least in the United States) it has been necessary to divide surgery into subspecialties. Whether for better or for worse, the "general surgeon" of a very recent day more and

[2]TEXTBOOK OF GENERAL SURGERY. By Warren H. Cole, M.D., F.A.C.S., and Robert Elman, M.D., F.A.C.S. Foreword by Evarts A. Graham, M.D., F.A.C.S. 6th ed. New York: Appleton-Century-Crofts, Inc., 1952.

more is approaching the status of a rarity. Reading of the volume at hand emphasizes the fact that no one man today can possibly keep abreast of all the developments in all the fields which formerly were included in the purlieu of the general surgeon.

EDWARD S. JUDD, JR.

A most successful textbook, *Gynecologic and Obstetric Pathology*,[1] retains the division into chapters and sequence of topics of the previous edition but revisions have been made in all except 5 chapters. The author's efforts to keep his book abreast of new developments and changing concepts are apparent.

There is extensive revision and addition to such timely topics as changes in the endocervical epithelium of the cervix in pregnancy, preinvasive squamous cell carcinoma of the cervix, the need for clinical classification of carcinoma of the endometrium, and the problems encountered in the microscopic study of hydatidiform mole and chorionepithelioma. Controversial phases of these and other topics are fairly presented and the author's opinions are clearly given.

Additional significant changes in the text include at least a brief discussion, for the sake of completeness, of the less common entities omitted in previous editions, appropriate new references, and numerous new illustrations. The proved value of the book as an atlas is increased with more than 80 additional illustrations as well as 16 replacements.

Finally, the value of this book is enhanced by a new chapter devoted to a summarizing discussion of common breast lesions which should prove useful in interpretation of the findings obtained in this essential part of the examination of women.

This revised edition will be even more valuable in our teaching of gynecologic and obstetric pathology to both graduate and undergraduate students.

JOHN I. BREWER.

[1] GYNECOLOGIC AND OBSTETRIC PATHOLOGY WITH CLINICAL AND ENDOCRINE RELATIONS. By Emil Novak, A.B., M.D., D.Sc., (Hon.), F.A.C.S., F.R.C.O.G. (Hon.). 3rd ed. Philadelphia, London: W. B. Saunders Co., 1952.

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Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

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